NÁDIA EMI AIKAWA

**Autoanticorpos órgão-específicos e sistêmicos em pacientes
com lúpus eritematoso sistêmico juvenil e dermatomiosite
juvenil**

Dissertação apresentada à Faculdade de
Medicina da Universidade de São Paulo para
obtenção do título de Mestre em Ciências

Programa de: Pediatria

Orientadora: Dra. Adriana Maluf Elias Sallum

**São Paulo
2011**

Dados Internacionais de Catalogação na Publicação (CIP)

Preparada pela Biblioteca da
Faculdade de Medicina da Universidade de São Paulo

©reprodução autorizada pelo autor

Aikawa, Nádia Emi

Autoanticorpos órgão-específicos e sistêmicos em pacientes com lúpus
eritematoso sistêmico juvenil e dermatomiosite juvenil / Nádia Emi Aikawa.

-- São Paulo, 2011.

Dissertação(mestrado)--Faculdade de Medicina da Universidade de
São Paulo.

Programa de Pediatria.

Orientadora: Adriana Maluf Elias Sallum.

Descritores: 1.Lúpus eritematoso sistêmico 2.Dermatomiosite juvenil
3.Autoanticorpos 4.Especificidade de órgãos

USP/FM/DBD-004/11

DEDICATÓRIA

À minha família, pelo carinho e dedicação em minha criação e pelo incentivo aos estudos.

AGRADECIMENTOS

À Dra Adriana Maluf Elias Sallum, por ter me orientado com muito carinho e apoio em todos os momentos e pelas preciosas contribuições ao estudo.

Ao Prof. Dr. Clovis Artur Almeida da Silva, por ser um exemplo em minha formação em Reumatologia Pediátrica, pelos incentivos incansáveis e contribuições valiosas ao estudo.

À Profa. Dra. Magda Carneiro-Sampaio, por ter possibilitado a realização deste estudo e pelo carinho e entusiasmo constantes.

À Dra. Bernadete de Lourdes Liphaus, pela idealização do estudo juntamente com a Profa. Magda e pelas importantes sugestões.

À Dra Adriana Almeida de Jesus, pelo auxílio inestimável na coleta de dados, por sua preciosa amizade e por ter me incentivado a fazer Reumatologia Pediátrica.

Aos amigos da Reumatologia Pediátrica, pelo carinho e paciência.

À bibliotecária Mariza Kazue Umetsu Yoshikawa, pela alegria e eficiência inabaláveis.

Aos colegas do Serviço de Arquivo Médico, pela simpatia e prontidão no empréstimo de prontuários.

Aos pacientes do Ambulatório de Reumatologia Pediátrica do Instituto da Criança HCFMUSP, que possibilitaram a realização deste estudo.

Esta dissertação está de acordo com as seguintes normas, em vigor no momento desta publicação:

Referências: adaptado de *International Committee of Medical Journals Editors* (Vancouver)

Universidade de São Paulo. Faculdade de Medicina. Serviço de Biblioteca e Documentação. *Guia de apresentação de dissertações, teses e monografias*. Elaborado por Anneliese Carneiro da Cunha, Maria Julia de A. L. Freddi, Maria F. Crestana, Marinalva de Souza Aragão, Suely Campos Cardoso, Valéria Vilhena. 2^a ed. São Paulo: Serviço de Biblioteca e Documentação; 2005.

Abreviaturas dos títulos dos periódicos de acordo com *List of Journals Indexed in Index Medicus*.

SUMÁRIO

SUMÁRIO

Lista de abreviaturas
Lista de tabelas
Resumo
Summary

1	Introdução.....	2
2	Objetivos.....	5
3	Métodos.....	7
4	Resultados.....	13
4.1	Dados demográficos.....	13
4.2	Autoanticorpos órgão-específicos e outros autoanticorpos.....	13
4.3	Doenças autoimunes órgão-específicas.....	17
5	Discussão.....	20
6	Conclusões.....	24
7	Referências.....	26
8	Anexos.....	30

LISTAS

ABREVIATURAS

JSLE	Lúpus eritematoso sistêmico juvenil
JDM	Dermatomiosite juvenil
TH	Tireoidite de Hashimoto
DM1	Diabetes melito tipo 1
DC	Doença celíaca
Anti-TPO	Anticorpo antiperoxidase tiroideana
Anti-Tg	Anti-tireoglobulina
TRAb	Anti-receptor de hormônio tireoestimulante (TSH)
IAA	Anti-insulina
Anti-GAD	Anti-descarboxilase do ácido glutâmico
Anti-LKM-1	Anticorpo microssomal rim-fígado tipo 1
AML	Anticorpo anti-músculo liso
AMA	Anti-mitocôndria
ACP	Anticorpo anti-célula parietal
EMA	Anticorpo anti-endomísio

TABELAS

- Tabela 1** – Autoanticorpos e doenças órgão-específicas e outros autoanticorpos em pacientes com lúpus eritematoso sistêmico juvenil (LESJ) *versus* pacientes com dermatomiosite juvenil (DMJ) 14
- Tabela 2** – Dados demográficos, atividade da doença, tratamento e outros autoanticorpos em pacientes com lúpus eritematoso sistêmico juvenil (LESJ) e dermatomiosite juvenil (DMJ) com e sem autoanticorpos órgão-específicos..... 16
- Tabela 3** – Dados demográficos, atividade da doença, outros autoanticorpos e tratamento em quatro pacientes com lúpus eritematoso sistêmico juvenil (LESJ) com doenças autoimunes órgão-específicas..... 18

RESUMO

Aikawa NA. Autoanticorpos órgão-específicos e sistêmicos em pacientes com lúpus eritematoso sistêmico juvenil e dermatomiosite juvenil [dissertação]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2011. 28p.

Objetivo: Ao nosso conhecimento, não há estudos na literatura avaliando simultaneamente um grande número de autoanticorpos órgão-específicos, bem como a prevalência de doenças autoimunes órgão-específicas em populações com lúpus eritematoso sistêmico juvenil (LESJ) e dermatomiosite juvenil (DMJ). Portanto, o objetivo deste estudo foi avaliar autoanticorpos e doenças autoimunes órgão-específicas em pacientes com LESJ e DMJ. **Métodos:** Quarenta e um pacientes com LESJ e 41 com DMJ foram investigados para os autoanticorpos séricos associados com hepatite autoimune, cirrose biliar primária, diabetes melito tipo 1 (DM1), tireoidite autoimune, gastrite autoimune e doença celíaca. Pacientes com positividade para anticorpos órgão-específicos foram avaliados para a presença das respectivas doenças autoimunes órgão-específicas. **Resultados:** A média de idade ao diagnóstico foi significativamente maior em pacientes com LESJ em comparação com DMJ ($10,3 \pm 3,4$ vs. $7,3 \pm 3,1$ anos, $p=0,0001$), enquanto a média de duração da doença foi similar em ambos os grupos ($p=0,92$). As freqüências de autoanticorpos órgão-específicos foram semelhantes nos pacientes com LESJ e DMJ ($p>0,05$). Notavelmente, uma alta prevalência de autoanticorpos relacionados a tireoidite autoimune e DM1 e foi observada em ambos os grupos (20% vs. 15%, $p=0,77$ e 24% vs. 15%, $p=0,41$, respectivamente). A elevada freqüência de fator anti-núcleo - FAN (93% vs. 59%, $p=0,0006$), anti-DNA (61% vs. 2%, $p<0,0001$), anti-Ro (35% vs. 0%, $p<0,0001$), anti-Sm ($p=0,01$), anti-RNP ($p=0,02$), anti-La ($p=0,03$) e aCL IgG ($p=0,001$) foram observadas em pacientes com LESJ em comparação com DMJ. Doenças autoimunes órgão-específicas foram evidenciadas apenas em pacientes com LESJ (24% vs. 0%, $p=0,13$). Dois pacientes com LESJ apresentavam DM1

associada com tireoidite de Hashimoto e um terceiro paciente apresentava tireoidite subclínica. Outro paciente com LESJ preenchia diagnóstico de doença celíaca com base em anemia por deficiência de ferro, a presença de anticorpo anti-endomísio, biópsia duodenal compatível com doença celíaca e resposta a dieta livre de glúten.

Conclusão: Doenças órgão-específicas foram observadas apenas em pacientes com LESJ e exigiram tratamento específico. A presença destes anticorpos sugere a avaliação de doenças órgão-específicas e um acompanhamento rigoroso destes pacientes.

Descritores: 1.Lúpus eritematoso sistêmico, 2.dermatomiosite juvenil, 3.autoanticorpos, 4.especificidade de órgãos

SUMMARY

Aikawa NE. Organ-specific and systemic autoantibodies in patients with juvenile systemic lupus erythematosus and juvenile dermatomyositis [dissertation]. São Paulo: "Faculdade de Medicina, Universidade de São Paulo"; 2010. 29p.

Objective: To our knowledge, no study has assessed simultaneously a large number of organ-specific autoantibodies, as well as the prevalence of organ-specific autoimmune diseases in juvenile systemic lupus erythematosus (JSLE) and juvenile dermatomyositis (JDM) populations. Therefore, the purpose of this study was to evaluate organ-specific autoantibodies and autoimmune diseases in JSLE and JDM patients.

Methods: Forty-one JSLE and 41 JDM patients were investigated for serum autoantibodies associated with autoimmune hepatitis, primary biliary cirrhosis, type 1 diabetes mellitus (T1DM), autoimmune thyroiditis, autoimmune gastritis and celiac disease. Patients with positive organ-specific antibodies were assessed for the presence of the respective organ-specific autoimmune diseases. **Results:** Mean age at diagnosis was significantly higher in JSLE compared to JDM patients (10.3 ± 3.4 vs. 7.3 ± 3.1 years, $p=0.0001$), whereas the mean disease duration was similar in both groups ($p=0.92$). The frequencies of organ-specific autoantibodies were similar in JSLE and JDM patients ($p>0.05$). Of note, a high prevalence of autoantibodies related to T1DM and autoimmune thyroiditis were observed in both groups (20% vs. 15%, $p=0.77$ and 24% vs. 15%, $p=0.41$; respectively). Higher frequencies of antinuclear antibody - ANA (93% vs. 59%, $p=0.0006$), anti-dsDNA (61% vs. 2%, $p<0.0001$), anti-Ro (35% vs. 0%, $p<0.0001$), anti-Sm ($p=0.01$), anti-RNP ($p=0.02$), anti-La ($p=0.03$) and IgG aCL ($p=0.001$) were observed in JSLE compared to JDM patients. Organ-specific autoimmune diseases were evidenced only in JSLE patients (24% vs. 0%, $p=0.13$). Two JSLE patients had T1DM associated with Hashimoto thyroiditis and another had subclinical thyroiditis. Another JSLE patient had celiac disease diagnosis based on iron deficiency anaemia, presence of anti-endomysial antibody, duodenal biopsy compatible to celiac disease and response to a gluten-free diet.

Conclusion: Organ-specific diseases were observed solely in JSLE patients and required specific therapy. The presence of these antibodies recommends the evaluation of organ-specific diseases and a rigorous follow-up of these patients.

Descriptors: 1.Systemic lupus erythematosus, 2.juvenile dermatomyositis, 3.autoantibodies, 4.specificity to organs

1 INTRODUÇÃO

O lúpus eritematoso sistêmico (LES) é uma doença autoimune multissistêmica, caracterizada pela presença de autoanticorpos circulantes^{1,2}. A dermatomiosite juvenil (DMJ) é uma doença do tecido conjuntivo caracterizada por vasculite muscular e cutânea, podendo também comprometer outros órgãos e sistemas³. A etiologia da DMJ é desconhecida. No entanto, a presença de inflamação muscular crônica, a positividade para autoanticorpos séricos e a associação com outras doenças autoimunes sugerem que um mecanismo autoimune esteja envolvido em sua fisiopatologia³.

Notavelmente, estudos sobre autoimunidade órgão-específica em pacientes com LES juvenil (LESJ) mostraram uma alta prevalência de anticorpos anti-insulina⁴, anti-tireóide e hipotireoidismo subclínico². Além disso, hepatite autoimune foi raramente relatada em nossos pacientes com LESJ⁵. Por outro lado, poucos estudos têm descrito anticorpos específicos para órgãos na DMJ^{6,7}, incluindo raros casos de tireoidite de Hashimoto (TH)⁸ e diabetes melito tipo 1 (DM1)⁹. Um aspecto relevante é que outras doenças autoimunes órgão-específicas, como doença celíaca (DC), gastrite autoimune e cirrose biliar primária, não foram avaliadas em ambas as doenças. Além disso, nenhum estudo avaliou simultaneamente um grande número de autoanticorpos órgão-específicos, bem como a prevalência de

---

doenças autoimunes órgão-específicas subclínicas em pacientes com LESJ e DMJ.

---

2 OBJETIVOS

---

1. Avaliar a prevalência de autoanticorpos séricos órgão-específicos em pacientes com LESJ e com DMJ.
  2. Avaliar a possível associação entre dados demográficos, atividade da doença e tratamento de pacientes com LESJ e com DMJ de acordo com a presença de autoanticorpos órgão-específicos.
  3. Descrever as doenças autoimunes órgão-específicas associadas em pacientes com LESJ e DMJ.
-

3 MÉTODOS

Pacientes e métodos

Quarenta e um pacientes com LESJ e 41 com DMJ regularmente acompanhados na Unidade de Reumatologia Pediátrica do Instituto da Criança do Hospital das Clínicas (HC) da Faculdade de Medicina da Universidade de São Paulo (FMUSP) foram selecionados entre janeiro de 2008 e janeiro de 2009. Todos os pacientes preencheram os critérios do *American College of Rheumatology* (ACR) para LESJ¹⁰ e de *Bohan & Peter* para DMJ¹¹. O Comitê de Ética do HC-FMUSP aprovou este estudo e um consentimento informado foi obtido de todos os participantes e de seus responsáveis.

Autoanticorpos órgão-específicos e outros autoanticorpos

Autoanticorpos séricos associadas com as seguintes doenças autoimunes órgão-específicas foram avaliados: **tireoidite autoimune** - anticorpo antiperoxidase tiroideana (anti-TPO) por fluoroimunoensaio e anticorpos anti-tireoglobulina (anti-Tg) e anti-receptor de hormônio tireoestimulante (TSH) (TRAb) por quimioluminescência; **DM1** - anticorpo anti-insulina (IAA), anti-descarboxilase do ácido glutâmico (anti-GAD) e anticorpo anti-tirosina

---

---

fosfatase (anti-IA2) por radioimunoensaio; **hepatite autoimune** – anticorpo microssomal rim-fígado tipo 1 (anti-LKM-1) e anticorpo anti-músculo liso (AML) por imunofluorescência indireta em fígado de rato e cortes de tecido renal; **cirrose biliar primária** – anti-mitocôndria (AMA) por imunofluorescência indireta em fígado, rins e células parietais de estômago de rato, e confirmação dos casos positivos por teste imunoenzimático (ELISA); **gastrite autoimune** - anticorpo anti-célula parietal (ACP) por imunofluorescência indireta; **doença celíaca** - anticorpo anti-endomísio (EMA) da classe IgA por imunofluorescência indireta. Os pacientes que foram positivos para os autoanticorpos órgão-específicos repetiram o teste para confirmação. Em seguida, foram investigados para a presença da doença autoimune órgão-específica.

Os seguintes anticorpos séricos também foram avaliados: fator anti-núcleo (FAN) por imunofluorescência indireta utilizando células de epiteloma humano (HEp-2), fator reumatóide (FR) por imunonefelometria, anti-DNA dupla-hélice (anti-dsDNA), anti-Sm, anti-RNP, anti-SSB/La anti-SSA/Ro, anti-topoisomerase-1 (anti-Scl70), anticardiolipina (aCL) isotipos IgG e IgM por ELISA e anticoagulante lúpico (LAC) pelo teste do veneno de víbora de Russel diluído e os testes confirmatórios, anticorpo anti-citoplasma de neutrófilos (ANCA) por ELISA e por imunofluorescência direta em neutrófilos humanos fixados com etanol e anti-Jo1 por ELISA. Todos os anticorpos foram avaliados na Divisão de Laboratório Central do HC-FMUSP.

Doenças autoimunes órgão-específicas

HT foi definida de acordo com a redução dos níveis de tiroxina livre (T4) e níveis elevados de TSH, e hipotireoidismo subclínico como níveis elevados de TSH associados a níveis normais de T4 livre¹². A presença de anticorpos anti-tireoidianos foi necessária para caracterizar a tireoidite autoimune. DM1 foi diagnosticada pela presença de poliúria, polidipsia e perda de peso sem causa definida, e glicose plasmática, ≥ 200 mg/dL a qualquer hora do dia ou glicemia de jejum ≥ 126 mg/dL¹³. Hepatite autoimune foi definida como uma hepatite crônica progressiva de origem desconhecida, caracterizada por níveis elevados de transaminases, hipergamaglobulinemia, autoanticorpos séricos e características histológicas¹⁴. Cirrose biliar primária foi definida como a presença de pelo menos dois dos seguintes: elevação de fosfatase alcalina (≥ 2 vezes o limite superior do normal) ou gama-glutamilttransferase (≥ 5 vezes o limite superior do normal), positividade para AMA e biópsia hepática com colangite supurativa e destruição de ductos biliares¹⁵. Gastrite autoimune foi definida pela presença atrofia de fundo e corpo gástrico à histologia, a positividade para o anticorpo APC e anti-fator intrínseco, hipo/acloridria, baixas concentrações de pepsinogênio sérico e anemia secundária a deficiência de vitamina B12 e ferro¹⁶. O diagnóstico da doença celíaca foi definido pela presença de pelo menos quatro dos seguintes critérios: quadro clínico (diarréia crônica, nanismo e/ou anemia ferropriva), positividade para anticorpos da classe IgA para doença celíaca, genótipo HLA-DQ2 ou DQ8, biópsia do intestino delgado compatível com enteropatia celíaca, e resposta a dieta livre de glúten¹⁷.

Atividade da doença, dano da doença e tratamento dos pacientes com LESJ e DMJ

A atividade do LESJ e dano cumulativo foram avaliados no momento da avaliação dos anticorpos e das doenças órgão-específicas nos pacientes com LESJ usando o *SLE Disease Activity Index 2000* (SLEDAI-2K)¹⁸ e o *Systemic Lupus International Collaborating Clinics/ACR Damage Index* (SLICC/ACR-DI)¹⁹. A atividade da DMJ foi avaliada pelo *Disease Activity Score* (DAS)²⁰ e a força muscular foi avaliada pelo *Childhood Myositis Assessment Scale* (CMAS) e o *Manual Muscle Testing* (MMT)²¹. As enzimas musculares dosadas concomitantemente aos anticorpos e doenças órgão-específicas foram: creatinofosfoquinase (CPK), aspartato aminotransferase (AST), alanina aminotransferase (ALT), desidrogenase láctica (DHL) e aldolase. Dados relativos aos tratamentos atuais do LESJ e DMJ foram: uso de prednisona e/ou imunossupressores (azatioprina, metotrexato, cloroquina, ciclosporina, ciclofosfamida, imunoglobulina intravenosa e micofenolato mofetil).

Análise estatística

Os resultados foram apresentados como média $\pm$ desvio padrão ou mediana (variação) para variáveis contínuas e número (%) para variáveis categóricas. As variáveis foram comparadas pelos testes t-Student ou Mann-Whitney para variáveis contínuas para avaliar as diferenças entre pacientes com

---

LESJ e DMJ. Para variáveis categóricas, as diferenças foram avaliadas pelo teste exato de Fisher. Em todos os testes estatísticos, o nível de significância foi fixado em 5% ($p < 0,05$).

---

4 RESULTADOS

4.1 Dados demográficos

A média de idade ao diagnóstico de LESJ foi significativamente maior em comparação com a de pacientes com DMJ ($10,3 \pm 3,4$ *versus* $7,3 \pm 3,1$ anos, $p=0,0001$). No entanto, a média de duração da doença foi semelhante nos dois grupos ($4,4 \pm 3,7$ *versus* $4,4 \pm 3,3$ $p=0,92$), bem como a frequência do sexo feminino (85% *versus* 71%, $p=0,18$).

4.2 Autoanticorpos órgão-específicos e outros autoanticorpos

As frequências de pelo menos um anticorpo sérico órgão-específico foram semelhantes nos pacientes com LESJ e DMJ [17 (41%) *versus* 11 (27%), $p=0,24$]. Altas frequências de autoanticorpos relacionados a tireoidite autoimune (anti-Tg, anti-TPO e/ou TRAb) e DM1 (anticorpos IAA, anti-GAD e/ou anti-IA2) foram observados em ambas as doenças (24% *versus* 15%, $p=0,41$, 20% *versus* 15%, $p=0,77$, respectivamente). As frequências de EMA e ACP foram comparáveis em ambos os grupos (2% *versus* 2%, $p=1,0$; 2% *versus* 0%, $p=1,0$, respectivamente). Da mesma forma, as frequências de anticorpos para hepatite autoimune foram semelhantes: anticorpo anti-LKM-1 e/ou AML (2% *versus* 5%, $p=1,0$). Nenhum dos pacientes com LESJ e DMJ apresentou AMA (Tabela 1).

Uma elevada frequência de FAN (93% *versus* 59%, $p=0,0006$), anti-dsDNA (61% *versus* 2%, $p<0,0001$), anti-Ro (35% *versus* 0%, $p<0,0001$), anti-Sm (27% *versus* 5%, $p=0,01$), anti-RNP (22% *versus* 2%, $p=0,02$), anti-La (15% *versus* 0%, $p=0,03$) e aCL IgG (46% *versus* 12%, $p=0,001$) foram observadas em pacientes com LESJ em comparação com DMJ (Tabela 1).

Tabela 1 – Autoanticorpos e doenças órgão-específicas e outros autoanticorpos em pacientes com lúpus eritematoso sistêmico juvenil (LESJ) versus pacientes com dermatomiosite juvenil (DMJ)

Variáveis	LESJ n=41	DMJ n=41	p
Anticorpos órgão-específicos	17 (41)	11 (27)	0,24
Tireoidite autoimune (anti-Tg e/ou anti-TPO e/ou TRAb)	10 (24)	6 (15)	0,41
Diabetes melito tipo 1 (IAA e/ou anti-GAD e/ou anti-IA2)	8 (20)	6 (15)	0,77
Doença celíaca (EMA)	1 (2)	1 (2)	1,0
Hepatite autoimune (AML e/ou anti-LKM-1)	1 (2)	2 (5)	1,0
Cirrose biliar primária (AMA)	0 (0)	0 (0)	1,0
Gastrite autoimune (ACP)	1 (2)	0 (0)	1,0
Doenças órgão-específicas	4/17 (24)	0/11 (0)	0,13
Outros autoanticorpos			
FAN	38 (93)	24 (59)	0,0006
FR	4 (10)	0 (0)	0,12
Anti-dsDNA	25 (61)	1 (2)	< 0,0001
Anti-Sm	11 (27)	2 (5)	0,01
Anti-RNP	9 (22)	1 (2)	0,02
Anti-Ro	14 (35)	0 (0)	< 0,0001
Anti-La	6 (15)	0 (0)	0,03
Anti-Scl-70	0 (0)	0 (0)	1,0
Anti-Jo1	0 (0)	2 (5)	0,49
aCL-IgM	20 (49)	17 (41)	0,66
aCL-IgG	19 (46)	5 (12)	0,001
LAC	5 (12)	1 (2)	0,2
ANCA-p	4 (10)	0 (0)	0,12
ANCA-c	1 (2)	1 (2)	1,0

Os dados estão expressos em n (%); anti-TPO - anticorpo antiperoxidase tiroideana, anti-Tg - anticorpo anti-tireoglobulina, TRAb - anti-receptor de hormônio tireoestimulante (TSH), IAA - anticorpo anti-insulina, anti-GAD - anti-descarboxilase do ácido glutâmico, anti-IA2 - anticorpo anti-tirosina fosfatase, anti-LKM-1 - anticorpo microssomal rim-fígado tipo 1, AML - anticorpo anti-músculo liso, AMA - anti-mitocôndria, ACP - anticorpo anti-célula parietal, EMA - anticorpo anti-endomísio, FAN - fator anti-núcleo, FR - fator reumatóide, anti-Scl70 - anti-topoisomerase 1, aCL - anticardiolipina, LAC - anticoagulante lúpico, ANCA-p - anticorpo anti-citoplasma de neutrófilos padrão perinuclear, anti-mieloperoxidase; ANCA-c - anticorpo anti-citoplasma de neutrófilos padrão citoplasmático, anti-proteinase-3

Não foram observadas diferenças em relação aos dados demográficos, atividade da doença, tratamento e freqüências de outros autoanticorpos em 17 pacientes com LESJ com pelo menos um anticorpo órgão-específico em relação a 24 pacientes que não apresentavam estes anticorpos ($p > 0,05$) (Tabela 2).

Além disso, nenhuma diferença foi evidenciada nos dados demográficos, atividade da doença, tratamento e outros auto-anticorpos em 11 pacientes com DMJ e pelo menos um anticorpos órgão-específico comparados com 30 sem anticorpos órgão-específicos ($p > 0,05$) (Tabela 2).

Tabela 2 – Dados demográficos, atividade da doença, tratamento e outros autoanticorpos em pacientes com lúpus eritematoso sistêmico juvenil (LESJ) e dermatomiosite juvenil (DMJ) com e sem autoanticorpos órgão-específicos

<i>Variáveis no LESJ</i>	LESJ com anticorpo órgão-específico (n=17)	LESJ sem anticorpo órgão-específico (n=24)	p
Dados demográficos			
Sexo feminino	13 (76)	22 (92)	0,21
Idade atual, anos	11 (4-13)	11 (6-17)	0,18
Duração da doença, anos	3,1 (0,3-7,6)	3,8 (0-12,3)	0,78
SLEDAI-2K	5 (0-12)	3 (0-14)	0,36
SLICC/ACR-DI	1 (0-2)	1 (0-2)	0,93
Tratamento atual			
Uso de prednisona	14 (83)	23 (96)	0,29
Uso de imunossupressor	7 (41)	17 (71)	0,11
Outros autoanticorpos			
FAN	15 (88)	23 (96)	0,56
anti-dsDNA	11 (65)	14 (58)	0,75
anti-Sm	6 (35)	5 (21)	0,48
anti-RNP	5 (29)	4 (17)	0,45
anti-Ro	8 (47)	6 (25)	0,19
anti-La	3 (18)	3 (13)	0,68
aCL-IgM	10 (59)	11 (46)	1,69
aCL-IgG	7 (41)	12 (50)	0,75
<i>Variáveis na DMJ</i>	DMJ com anticorpo órgão-específico (n=11)	DMJ sem anticorpo órgão-específico (n=30)	p
Dados demográficos			
Sexo feminino	10 (91)	19 (63)	0,13
Idade atual, anos	12 (5-17)	11 (6-18)	0,92
Duração da doença, anos	3,7 (1,1-8,1)	3,7 (0-13,5)	0,86
Escores de DMJ e enzimas musculares			
CMAS (0 - 52)	50 (44-52)	48,5 (4-52)	0,27
MMT (0 - 80)	80 (75-80)	80 (38-80)	0,47
DAS (0 - 20)	2 (0-7)	3 (0-17)	0,71
AST (10 – 36 UI/L)	23,5 (12-43)	25,5 (14-90)	0,57
ALT (24 – 49 UI/L)	34 (29-103)	33,5 (10-123)	0,76
CPK (39 – 170 UI/L)	93 (26-165)	92,5 (40-27381)	0,72
Aldolase (<7,6 UI/L)	7,05 (3,5-9,4)	7,2 (2,7-49,9)	0,95
DHL (240 – 480 UI/L)	159,5 (135-238)	200 (87-522)	0,19
Tratamento atual			
Uso de prednisona	6 (55)	15 (50)	1,0
Uso de imunossupressor	7 (64)	17 (57)	0,74
Outros autoanticorpos			
FAN	5 (45)	19 (63)	0,48
aCL-IgM	5 (45)	12 (40)	1,0

Dados expressos em n (%) ou mediana (variação); SLEDAI-2K - *Systemic Lupus Erythematosus Disease Activity Index 2000*, SLICC/ACR-DI-*Systemic Lupus International Collaborating Clinics/ACR Damage Index*, FAN - fator anti-núcleo, aCL – anticardiolipina, CMAS - *Childhood Muscle Assessment Score*, MMT - *Manual Muscle Testing*, DAS - *Disease Activity Score*, AST - aspartato aminotransferase, ALT - alanina aminotransferase, CPK - creatinofosfoquinase, DHL - desidrogenase láctica.

4.3 Doenças autoimunes órgão-específicas

Doenças autoimunes órgão-específicas foram evidenciadas apenas em pacientes com LESJ (24% *versus* 0%, $p=0,13$) (Tabela 1). Dois destes pacientes preencheram critérios diagnósticos de DM1 e HT e foram tratados com insulina e levotiroxina. Outro paciente apresentava hipotireoidismo subclínico com positividade para anticorpo anti-Tg. O quarto paciente preencheu diagnóstico de doença celíaca com base nas seguintes características: anemia por deficiência crônica de ferro, presença de anticorpo EMA, biópsia duodenal compatível com doença celíaca e resposta a dieta sem glúten (Tabela 3). Nenhum dos 41 pacientes com DMJ apresentou evidências de doenças autoimunes órgão-específicas.

Tabela 3 – Dados demográficos, atividade da doença, outros autoanticorpos e tratamento em quatro pacientes com lúpus eritematoso sistêmico juvenil (LESJ) com doenças autoimunes órgão-específicas

Caso	1	2	3	4
Dados demográficos				
Idade ao diagnóstico de LESJ, anos	11,6	15,6	11,1	9,3
Idade ao diagnóstico da doença autoimune órgão-específica, anos	11,4	12	11,6	13,2
Idade atual, anos	15	18,9	16,3	12,6
Sexo	feminino	feminino	feminino	feminino
Doença autoimune órgão-específica	DM1 e TH	DM1 e TH	Hipotireoidismo subclínico	Doença celíaca
Anticorpos órgão-específicos	Anti-TPO e IAA	TRAb, IAA e Anti-GAD	Anti-Tg	EMA
Características clínicas ao diagnóstico de LESJ				
Envolvimento mucocutâneo	-	+	-	+
Artrite	+	-	+	-
Serosite	+	-	+	+
Anormalidades hematológicas	-	+	+	-
Envolvimento neuropsiquiátrico	-	-	-	-
Nefrite	-	+	+	-
Atividade de doença e dano na avaliação dos anticorpos órgão-específicos				
SLEDAI-2K	8	8	12	8
SLICC/ACR-DI	2	1	1	0
Tratamento atual				
LESJ	Prednisona	Prednisona, cloroquina e azatioprina	Prednisona, cloroquina e azatioprina	Prednisona e cloroquina
Doença autoimune órgão-específica	Insulina e reposição de levotiroxina	Insulina e reposição de levotiroxina	-	Dieta livre de glúten

DM1 – diabetes melito tipo 1, TH – tireoidite de Hashimoto, anti-TPO - anticorpo antiperoxidase tiroideana, IAA – anti-insulina, TRAb - anti-receptor de hormônio tireoestimulante (TSH), anti-GAD - anti-descarboxilase do ácido glutâmico, anti-Tg - anti-tireoglobulina, EMA - anticorpo anti-endomísio, SLEDAI-2K - *Systemic Lupus Erythematosus Disease Activity Index 2000*, SLICC/ACR-DI - *Systemic Lupus International Collaborating Clinics/ACR (SLICC/ACR) Damage Index*, + positivo, - negativo

5 DISCUSSÃO

Este foi o primeiro estudo que avaliou simultaneamente uma variedade de anticorpos órgão-específicos em populações de LESJ e DMJ e demonstrou uma alta prevalência destes anticorpos em ambas as doenças. Outros anticorpos foram evidenciados exclusivamente em pacientes com lúpus. Assim como, doenças autoimunes órgão-específicas foram evidenciadas apenas em pacientes com LESJ, particularmente doenças endócrinas e gastrintestinais, que necessitaram de tratamento específico.

O LESJ é uma doença autoimune crônica multissistêmica, caracterizada pela presença de linfócitos auto-reativos e um risco acentuado para o desenvolvimento de múltiplos autoanticorpos órgão-específicos e não órgão-específicos². No presente estudo, o perfil de outros anticorpos específicos e não específicos foi claramente evidenciado nos pacientes com LESJ em relação à DMJ.

Tireoidite autoimune clínica, especialmente HT, é a mais importante doença autoimune órgão-específica no lúpus pediátrico em pacientes do sexo feminino. A frequência de anticorpos anti-tireóide foi previamente relatada em 14% a 26% desses pacientes^{2,22}, como observado neste estudo. Hipotireoidismo autoimune subclínico foi evidenciado em 0-7% da população com LESJ, como também observado neste estudo^{2,22}. Por outro lado, hipertireoidismo autoimune não foi diagnosticado em nosso estudo e já foi descrita em 2-3% destes pacientes^{2,22}.

Interessantemente, nenhum estudo avaliou a frequência de anticorpos associados a DM1 na população de LES, e, poucos relatos descreveram anticorpos contra o pâncreas em pacientes adultos e pediátricos com lúpus⁴. Nesta população, 5% dos pacientes com LESJ tinham anticorpos e DM1 insulino-dependente controlados. Esta doença autoimune é subdiagnosticada em pacientes com LESJ, provavelmente devido à alta frequência de diabetes melito induzido pelo uso de glicocorticóides.

Outro aspecto relevante deste estudo foi a avaliação da autoimunidade gástrica e intestinal. Surpreendentemente, um paciente com LESJ desta casuística, com anemia ferropriva crônica e sem manifestações gastrointestinais apresentava doença celíaca. Na realidade, as manifestações mais comuns desta doença são perda de peso e diarreia e anemia crônica é uma das manifestações extra-intestinais encontradas nas formas subclínicas da doença¹⁷.

O anticorpo ACP está altamente correlacionado com gastrite autoimune crônica¹⁶. Em um paciente deste estudo com LESJ e positividade para ACP, a ausência de manifestações gastrointestinais pode indicar que o processo autoimune estava em uma fase inicial. De fato, a alteração atrófica da mucosa gástrica pode evoluir para gastrite crônica autoimune em um período de 20 a 30 anos¹⁶, e esse paciente requer um acompanhamento rigoroso. Da mesma forma, neste estudo, três dos pacientes com LESJ e DMJ apresentavam anticorpos para o fígado, e também devem ser constantemente monitorados¹⁴.

Além disso, estudos anteriores com pequenas populações de DMJ e avaliações incompletas relataram a avaliação de anticorpos órgão-específicos e outros autoanticorpos. Observaram-se apenas anticorpos anti-hepáticos, endócrinos e intestinais em pacientes com DMJ, sem doenças autoimunes, como já descrito⁷. Montecucco et al⁶ não evidenciaram autoanticorpos hepáticos ou gástricos em 14 pacientes com DMJ, e Martinez-Cordero et al⁷ descreveram apenas um paciente com DMJ e AML. FAN e aCL IgM foram observados em quase 50% dos pacientes deste estudo, tendo o último apresentado uma frequência maior em comparação com estudos anteriores⁶.

A atividade de doença e tratamento não foram associados com autoanticorpos órgão-específicos nas duas populações de doenças autoimunes estudadas. Em contraste, uma alta frequência de anticorpos anti-tireóide e tireoidite subclínica foi anteriormente evidenciada em pacientes com LESJ leve². Além disso, a flutuação destes anticorpos pode ocorrer durante o curso da doença, como descrito no LESJ com doença autoimune da tireóide^{2,12}.

Em conclusão, doenças órgão-específicas foram observadas apenas em pacientes com LESJ e necessitaram de tratamento específico. A presença destes anticorpos recomenda a avaliação de doenças órgão-específicas e um acompanhamento rigoroso destes pacientes.

---

6 CONCLUSÕES

---

1. As prevalências de autoanticorpos órgão-específicos foram elevadas e semelhante entre pacientes com LSEJ e DMJ, predominando anticorpos associados a tireoidite autoimune e DM1.
  2. As prevalências de outros autoanticorpos (FAN, anti-DNA, anti-Sm, anti-RNP, anti-Ro, anti-La e aCL-IgG) foram estatisticamente mais elevadas no LESJ em relação à DMJ.
  3. Não houve associação entre dados demográficos, atividade da doença e tratamento de pacientes com LESJ e DMJ e a presença de autoanticorpos órgão-específicos.
  4. Doenças autoimunes órgão-específicas, particularmente endócrinas e gastrintestinais, foram observadas apenas em pacientes com LESJ.
-

7 REFERÊNCIAS

-
1. Faco MM, Leone C, Campos LM, Febrônio MV, Marques HH, Silva CA. Risk factors associated with the death of patients hospitalized for juvenile systemic lupus erythematosus. *Braz J Med Biol Res* 2007; 40: 993-1002.
  2. Parente Costa L, Bonfá E, Martinago CD, de Oliveira RM, Carvalho JF, Pereira RM. Juvenile onset Systemic Lupus Erythematosus thyroid dysfunction: a subgroup with mild disease? *J Autoimmun.* 2009; 33: 121-124.
  3. Sallum AME, Kiss MHB, Sachetti S, *et al.* Juvenile Dermatomyositis: clinical. laboratorial. histological. therapeutical and evolutive parameters of 35 patients. *Arq. Neuropsiquiatr.* 2002; 60: 889-899.
  4. Lidar M, Braf A, Givol N, *et al.* Anti-insulin antibodies and the natural autoimmune response in systemic lupus erythematosus. *Lupus* 2001; 10: 81-86.
  5. Deen ME, Porta G, Fiorot FJ, Campos LM, Sallum AM, Silva CA. Autoimmune hepatitis and juvenile systemic lupus erythematosus. *Lupus.* 2009; 18: 747-751.
  6. Montecucco C, Ravelli A, Caporali R, *et al.* Autoantibodies in juvenile dermatomyositis. *Clin Exp Rheumatol.* 1990; 8: 193-196.
  7. Martínez-Cordero E, Martínez-Miranda E, Aguilar León DE. Autoantibodies in juvenile dermatomyositis. *Clin Rheumatol.* 1993; 12: 426-428.
  8. Go T, Mitsuyoshi I. Juvenile dermatomyositis associated with subclinical hypothyroidism due to auto-immune thyroiditis. *Eur J Pediatr.* 2002; 161: 358-359.
-

-
9. Singh R, Cuchacovich R, Gomez R, Vargas A, Espinoza LR, Gedalia A. Simultaneous occurrence of diabetes mellitus and juvenile dermatomyositis: report of two cases. *Clin Pediatr*. 2003; 42: 459-62.
  10. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis and Rheumatism*. 1997; 40: 1725.
  11. Bohan A, Peter JB. Polymiositis and dermatomyositis. *N Engl J Med*. 1975; 13: 344-347.
  12. Franklyn JA. Hypothyroidism. *Medicine*. 2005; 33: 27-29.
  13. American Diabetes Association. Standards of medical care in diabetes 2007 (Positional Statement). *Diabetes Care*. 2007; 30: S4-S41.
  14. Alvarez F, Berg PA, Bianchi FB, *et al*. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol*. 1999; 31: 929-938.
  15. Kaplan MM, Gershwin ME. Primary biliary cirrhosis. *N Engl J Med*. 2005; 353: 1261-1273.
  16. De Block CE, De Leeuw IH, Van Gaal LF. Autoimmune gastritis in type 1 diabetes: a clinically oriented review. *J Clin Endocrinol Metab*. 2008; 93: 363-371.
  17. Catassi C, Fasano A. Celiac disease diagnosis: simple rules are better than complicated algorithms. *Am J Med*. 2010; 123: 691-693.
  18. Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol*. 2002; 29: 288-291.
  19. Brunner HI, Silverman ED, To T, Bombardier C, Feldman BM. Risk factors for damage in childhood-onset systemic lupus erythematosus: cumulative disease activity and medication use predict disease damage. *Arthritis Rheum*. 2002; 46: 436-444.
-

-
20. Bode RK, Klein-Gitelman MS, Miller ML, Lechman TS, Pachman LM. Disease activity score for children with juvenile dermatomyositis: reliability and validity evidence. *Arthritis Rheum.* 2003; 49: 7-15.
  21. Lovell DJ, Lindsley CB, Rennebohm RM, *et al.* Development of validated disease activity and damage indices for the juvenile idiopathic inflammatory myopathies. II. The Childhood Myositis Assessment Scale (CMAS): a quantitative tool for the evaluation of muscle function. The Juvenile Dermatomyositis Disease Activity Collaborative Study Group. *Arthritis Rheum.* 1999; 42: 2213-2219.
  22. Ronchezel MV, Len CA, Spinola e Castro A, *et al.* Thyroid function and serum prolactin levels in patients with juvenile systemic lupus erythematosus. *J Pediatr Endocrinol Metab.* 2001; 14: 165-169.
-

ANEXOS

Anexo I – “Organ-specific autoantibodies and autoimmune diseases in juvenile systemic lupus erythematosus and juvenile dermatomyositis patients”

Submetido à revista *Lupus*

Anexo II – “Penile and scrotum swellings in juvenile dermatomyositis”

Submetido à revista *Acta Reumatologica Portuguesa*

Anexo III – “Menstrual and hormonal alterations in juvenile dermatomyositis”

Publicado na revista *Clinical and Experimental Rheumatology*

Anexo IV – “Risk factors associated with calcinosis of juvenile dermatomyositis”

Publicado na revista *Jornal de Pediatria*

Anexo V – “Irreversible blindness in juvenile systemic lupus erythematosus”

Publicado na revista *Lupus*

Lupus - Manuscript ID LUP-11-023

1 message

---

editorial@lupusjournal.co.uk <editorial@lupusjournal.co.uk>

Thu, Jan 13, 2011 at
6:57 PM

To: nadia.aikawa@gmail.com

13-Jan-2011

Dear Dr. Aikawa:

Your manuscript entitled "ORGAN-SPECIFIC AUTOANTIBODIES AND AUTOIMMUNE DISEASES IN JUVENILE SYSTEMIC LUPUS ERYTHEMATOSUS AND JUVENILE DERMATOMYOSITIS PATIENTS" has been successfully submitted online and is being considered for processing.

Your manuscript ID is LUP-11-023.

Please quote the above manuscript ID in all future correspondence. If there are any changes in your street address or e-mail address, please log in to Manuscript Central at <http://mc.manuscriptcentral.com/lupus> and edit your user information as appropriate.

You can also view the status of your manuscript at any time by checking your Author Center after logging in to <http://mc.manuscriptcentral.com/lupus> .

Thank you very much for submitting your manuscript to Lupus.

Kind regards.

Yours sincerely

Denzil Fletcher
Lupus Editorial Office

Concise Report

ORGAN-SPECIFIC AUTOANTIBODIES AND AUTOIMMUNE DISEASES IN JUVENILE SYSTEMIC LUPUS ERYTHEMATOSUS AND JUVENILE DERMATOMYOSITIS PATIENTS

Nádia E. Aikawa^{1,2}, Adriana A. Jesus¹, Bernadete L. Liphaus¹, Clovis A. Silva^{1,2}, Magda Carneiro-Sampaio³, Adriana M.E. Sallum¹

Paediatric Rheumatology Unit¹, Rheumatology Division² and Immunology and Allergology Unit³ of Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

Conflicts of interest: none

Corresponding author:

Nádia Emi Aikawa

Rua Oscar Freire, 1456 - Apto 53

Jardim América – São Paulo – SP, Brazil

ZIP code: 05409-010

FAX: 00 55 11 3069-8503, E-mail – nadia.aikawa@gmail.com

Summary

To our knowledge, no study has assessed simultaneously a large number of organ-specific autoantibodies, as well as the prevalence of organ-specific autoimmune diseases in juvenile systemic lupus erythematosus (JSLE) and juvenile dermatomyositis (JDM) populations. Therefore, the purpose of this study was to evaluate organ-specific autoantibodies and autoimmune diseases in JSLE and JDM patients. Forty-one JSLE and 41 JDM patients were investigated for serum autoantibodies associated with autoimmune hepatitis, primary biliary cirrhosis, type 1 diabetes mellitus (T1DM), autoimmune thyroiditis, autoimmune gastritis and celiac disease. Patients with positive organ-specific antibodies were assessed for the presence of the respective organ-specific autoimmune diseases. Mean age at diagnosis was significantly higher in JSLE compared to JDM patients (10.3 ± 3.4 vs. 7.3 ± 3.1 years, $p=0.0001$), whereas the mean disease duration was similar in both groups ($p=0.92$). The frequencies of organ-specific autoantibodies were similar in JSLE and JDM patients ($p>0.05$). Of note, the high prevalence of autoantibodies related to T1DM and autoimmune thyroiditis were observed in both groups (20% vs. 15%, $p=0.77$ and 24% vs. 15%, $p=0.41$; respectively). Higher frequencies of antinuclear antibody - ANA (93% vs. 59%, $p=0.0006$), anti-dsDNA (61% vs. 2%, $p<0.0001$), anti-Ro (35% vs. 0%, $p<0.0001$), anti-Sm ($p=0.01$), anti-RNP ($p=0.02$), anti-La ($p=0.03$) and IgG aCL ($p=0.001$) were observed in JSLE compared to JDM patients. Organ-specific autoimmune diseases were evidenced only in JSLE patients (24% vs. 0%, $p=0.13$). Two JSLE patients had T1DM associated with Hashimoto thyroiditis and another had subclinical thyroiditis. Another JSLE patient had celiac disease diagnosis based on iron deficiency anaemia, presence of anti-endomysial antibody, duodenal biopsy compatible to celiac disease and response to a gluten-free diet. In conclusion, organ-specific diseases were observed solely in JSLE patients and required specific therapy. The presence of these antibodies recommends the evaluation of organ-specific diseases and a rigorous follow-up of these patients.

Keywords: organ-specific, autoantibodies, juvenile systemic lupus erythematosus, juvenile dermatomyositis.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune multisystemic disease characterized by the presence of autoantibodies¹. Juvenile dermatomyositis (JDM) is a connective tissue disease characterized by muscle and cutaneous vasculitis, which can also compromise other organs and systems². JDM etiology is unknown. However, the presence of chronic muscle inflammation, positivity for serum autoantibodies and association with other autoimmune diseases suggest that autoimmune mechanism is involved in its pathogenesis².

Of note, studies on organ-specific autoimmunity in juvenile SLE (JSLE) patients have shown a high prevalence of anti-thyroid antibodies and subclinical hypothyroidism¹. Additionally, autoimmune hepatitis was rarely reported in our JSLE patients³. On the other hand, few studies have described organ-specific antibodies in JDM^{4,5}, including rare cases of Hashimoto thyroiditis (HT)⁶ and type 1 diabetes mellitus (T1DM)⁷. To our knowledge, other organ-specific autoimmune diseases, such as celiac disease (CD), autoimmune gastritis and primary biliary cirrhosis, were not evaluated in both diseases.

Moreover, no study assessed simultaneously a large number of organ-specific autoantibodies, as well as the prevalence of subclinical organ-specific autoimmune diseases in JSLE and JDM patients.

Therefore, the objectives of the present study were to investigate the organ-specific and other serum autoantibodies in JSLE and JDM populations, and to evaluate the possible association between demographic data, disease activity and treatment in JSLE and JDM patients according to the presence of organ-specific antibodies. In addition, the organ-specific diseases were also described.

Patients and methods

Forty-one JSLE and 41 JDM patients regularly followed at the Pediatric Rheumatology Unit of our University Hospital were enrolled from January 2008 to January 2009. All patients fulfilled the American College of Rheumatology (ACR) criteria for JSLE⁸ and the Bohan and Peter criteria for JDM⁹. The Local Ethical Committee approved this study and an informed consent was obtained from all participants.

Organ-specific and other autoantibodies

Serum autoantibodies associated with the following organ-specific autoimmune diseases were assessed: **autoimmune thyroiditis** - anti-thyroid peroxidase (anti-TPO) antibody by fluoroimmunoassay, anti-thyroglobulin (anti-TG) antibody and anti-thyroid stimulating hormone (TSH) receptor antibody (TRAb) by chemiluminescence; **T1DM** - insulin autoantibody (IAA), anti-glutamic acid decarboxylase (anti-GAD) antibody and anti-tyrosine phosphatase (anti-IA2) antibody by radioimmunoassay; **autoimmune hepatitis** - anti-type I liver-kidney microsomal (anti-LKM-1) antibody and anti-smooth muscle antibody (SMA) by indirect immunofluorescence on rat liver and kidney tissue sections; **primary biliary cirrhosis** - antimitochondrial antibody (AMA) by indirect immunofluorescence on rat liver, kidney and stomach parietal cells, and confirmation of the positive cases by enzyme-linked immunosorbent assay (ELISA); **autoimmune gastritis** - parietal cell autoantibody (PCA) by indirect immunofluorescence; **celiac disease** – immunoglobulin A (IgA) class anti-endomysial (EMA) antibody by indirect immunofluorescence. Patients who were positive for organ-specific autoantibodies had the test repeated for confirmation. After that, they were investigated for the presence of the organ-specific autoimmune disease.

The following other serum autoantibodies were also measured: antinuclear antibody (ANA) by indirect immunofluorescence using human cell epithelioma (HEp-2), rheumatoid factor (RF) by immunonephelometry, anti-double-stranded DNA (anti-dsDNA), anti-Sm, anti-RNP, anti-SSA/Ro, anti-

SSB/La , anti-topoisomerase 1 (anti-Scl70), anticardiolipin (aCL) isotypes IgG and IgM by ELISA and lupus anticoagulant (LAC) by the dilute Russell's viper venom time with confirmatory testing, anti-neutrophil cytoplasm antibody (ANCA) by ELISA and direct immunofluorescence in human neutrophils fixed with ethanol and anti-Jo1 by ELISA.

All autoantibodies were assessed at Central Laboratory Division of our Hospital.

Organ-specific autoimmune diseases

HT was defined according to the reduced levels of free thyroxine (T4) and elevated TSH levels, and subclinical hypothyroidism as elevated TSH levels associated with normal levels of T4¹⁰. The presence of antithyroid antibodies was required to characterize autoimmune thyroiditis. T1DM was diagnosed by the presence of polyuria, polydipsia and unexplained weight loss, and increased plasma glucose ≥ 200 mg/dL at any time of day or fasting glucose ≥ 126 mg/dL¹¹. Autoimmune hepatitis was defined as a progressive chronic hepatitis of unknown origins, characterized by elevated transaminase levels, hypergammaglobulinemia, serum autoantibodies and histological characteristics¹². Primary biliary cirrhosis was defined as the presence of at least two of the following: elevated alkaline phosphatase (≥ 2 times the upper limit of normal) or gamma-glutamyltransferase (≥ 5 times the upper limit of normal), positivity for AMA, and liver biopsy with nonsuppurative cholangitis and destruction of bile ducts¹³. Autoimmune gastritis was defined by the presence of gastric fundus and body atrophy in histology, positivity for PCA and anti-intrinsic factor, hypo/achlorhydria, low concentrations of serum pepsinogen and anemia secondary to vitamin B12 and iron deficiency¹⁴. Celiac disease diagnosis was defined by the presence of at least four of the following criteria: clinical manifestations (chronic diarrhea, stunting and/or iron deficiency anemia), positivity for celiac disease IgA class antibodies, HLA-DQ2 or DQ8 genotype, small intestine biopsy compatible with celiac enteropathy, and response to gluten-free diet¹⁵.

Disease activity, disease damage and treatment in JSLE and JDM patients

SLE disease activity and cumulative damage were measured at the moment of organ-specific antibodies and disease evaluations in JSLE patients using the SLE Disease Activity Index 2000 (SLEDAI-2K)¹⁶ and the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SLICC/ACR-DI)¹⁷.

JDM activity was assessed by disease activity score (DAS)¹⁸, and muscle strength was evaluated by childhood myositis assessment scale (CMAS)¹⁹ and manual muscle testing (MMT)¹⁹. The serum muscle enzymes performed concomitantly to organ-specific antibodies and disease assessments were creatine phosphokinase (CPK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and aldolase.

Data concerning the current JSLE and JDM treatments included: prednisone, methotrexate, azathioprine, chloroquine, cyclosporine, cyclophosphamide, mycophenolate mofetil and intravenous immunoglobulin.

Statistical analysis

Results were presented as mean $\pm$ standard deviation or median (range) for continuous and number (%) for categorical variables. Data were compared by t-Student or Mann-Whitney tests for continuous variables to evaluate differences between JSLE and JDM patients. For categorical variables differences were assessed by Fisher's exact test. In all the statistical tests the level of significance was set at 5% ($p < 0.05$).

Results

Demographic features: The mean age at JSLE diagnosis was significantly higher compared to JDM patients (10.3 ± 3.4 vs. 7.3 ± 3.1 years, $p=0.0001$). However, the mean duration of disease was similar in both groups (4.4 ± 3.7 vs. 4.4 ± 3.3 , $p=0.92$), as well as the frequency of female gender (85% vs. 71%, $p=0.18$).

Organ-specific and other autoantibodies

The frequencies of at least one serum organ-specific antibody were similar in JSLE and JDM patients [17 (41%) vs. 11 (27%), $p=0.24$]. High frequencies of autoantibodies related to autoimmune thyroiditis (anti-TG, anti-TPO antibodies and/or TRAb) and T1DM (IAA, anti-GAD and/or anti-IA2 antibodies) were observed in both diseases (24% vs. 15%, $p=0.41$; 20% vs. 15%, $p=0.77$; respectively). The frequencies of EMA and PCA were comparable in both groups (2% vs. 2%, $p=1.0$; 2% vs. 0%, $p=1.0$; respectively). Likewise, the frequencies of autoimmune hepatitis antibodies were similar: anti-LKM-1 antibody and/or SMA (2% vs. 5%, $p=1.0$). None of JSLE and JDM patient had AMA (Table 1).

Higher frequencies of ANA (93% vs. 59%, $p=0.0006$), anti-dsDNA (61% vs. 2%, $p<0.0001$), anti-Ro (35% vs. 0%, $p<0.0001$), anti-Sm ($p=0.01$), anti-RNP ($p=0.02$), anti-La ($p=0.03$) and IgG aCL ($p=0.001$) were observed in JSLE compared to JDM patients (Table 1).

No differences were observed in the demographic data, disease activity, treatment and other autoantibodies frequencies in 17 JSLE patients with at least one organ-specific autoantibody compared to 24 without organ-specific autoantibodies ($p>0.05$) (Table 2). Additionally, no differences were evidenced in the demographic data, disease activity, treatment and other autoantibodies in 11 JDM patients with at least one organ-specific autoantibody *versus* 30 without organ-specific autoantibodies ($p>0.05$) (Table 2).

Organ-specific autoimmune diseases

Organ-specific autoimmune diseases were evidenced only in JSLE patients (24% vs. 0%, $p=0.13$) (Table 1). Two of them fulfilled both T1DM and HT diagnosis criteria and were treated with insulin and levothyroxine. Another patient had subclinical hypothyroidism with presence of anti-TG antibody. The fourth patient had diagnosis of celiac disease based on the following features: chronic iron deficiency anaemia, presence of AEM antibody, duodenal biopsy compatible to celiac disease and response to a gluten-free diet (Table 3).

None of our 41 JDM patients had evidence of organ-specific autoimmune diseases.

Discussion

As far as we know, this was the first study to evaluate simultaneously a variety of organ-specific antibodies in JSLE and JDM populations, and demonstrated a high prevalence of these antibodies in both diseases. Other antibodies were demonstrated in lupus patients, and organ-specific autoimmune diseases were evidenced exclusively in JSLE patients, particularly autoimmune endocrine and gastrointestinal illnesses that required specific treatment.

Of note, JSLE is a chronic multisystem autoimmune disease, characterized by the presence of autoreactive cells and a marked risk for the development of multiple organ and non-organ-specific autoantibodies¹. The profile of other specific and non-specific antibodies was clearly evidenced in our JSLE patients compared to JDM.

Clinical autoimmune thyroiditis, specially HT, is the most important organ-specific autoimmune disease in female pediatric lupus, and the frequency of anti-thyroid antibodies were previously reported in 14% to 26% of these patients^{1,20}, as observed in the current study. Autoimmune subclinical hypothyroidism was evidenced in 0-7% of JSLE population, as also observed herein^{1,20}. On the other hand, autoimmune hyperthyroidism was not diagnosed in our study and has been already described in 2-3% of these patients^{1,20}.

Interestingly, no study evaluated the frequency of T1DM-associated antibodies in JSLE population, and, to our knowledge, few reports have described pancreas autoantibodies in adult and pediatric lupus⁷. In our population, we found 5% of JSLE patients with these antibodies and controlled insulin-dependent T1DM. This autoimmune disease is under diagnosed in JSLE patients, probably due to a high frequency of diabetes mellitus induced by glucocorticoids use.

Other relevant aspect of our study was the assessment of gastric and intestinal autoimmunity. Remarkably, one of our JSLE patients with chronic iron deficient anemia and without gastrointestinal manifestations had CD. Indeed, the most common manifestations of CD are weight loss and diarrhea, and

chronic anemia is one of the extra-intestinal manifestations found in the subclinical forms of the disease¹⁵.

The PCA antibody is highly correlated with chronic autoimmune gastritis¹⁴. The absence of gastrointestinal manifestations may indicate that the autoimmune process was at an initial stage in one of our JSLE patients with PCA. Importantly, atrophic alteration of the gastric mucosa can progress to chronic autoimmune gastritis within 20 to 30 years period¹⁴, and this patient requires a rigorous follow-up. Likewise, three of our lupus and JDM patients had liver autoantibodies, and also should be constantly monitored¹².

Furthermore, previous studies were reported with small JDM populations and incomplete evaluations reported assessment of organ-specific and other antibodies. We observed only endocrine, liver and intestinal autoantibodies in JDM patients without autoimmune diseases, as previously described⁵. Montecucco et al⁴ did not evidence autoimmune liver and gastric autoantibodies in 14 JDM patients, and Martinez-Cordero et al⁵ described one JDM patient with SMA. ANA and aCL-IgM were observed in almost 50% of our patients, and the later had a higher frequency compared to previous studies⁴.

Disease activity and treatment was not associated with organ-specific autoantibodies in our two autoimmune disease populations. In contrast, a high frequency of anti-thyroid antibodies and subclinical thyroiditis were previously evidenced in mild JSLE patients¹. Moreover, fluctuation of these antibodies may occur during the course of the disease, as described in JSLE with autoimmune thyroid disease^{1,10}.

In conclusion, organ-specific diseases were observed solely in JSLE patients and required specific treatment. The presence of these antibodies recommends the evaluation of organ-specific diseases and a rigorous follow-up of these patients.

ACKNOWLEDGMENTS

This study was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo – FAPESP (grant #08/58238-4 to MCS), by Conselho Nacional de Desenvolvimento Científico e Tecnológico – CNPq (grant #300248/2008-3 to CAS) and Federico Foundation Grant to CAS. We thank Dr. Leila Antonângelo of Central Laboratory Division of our Hospital.

REFERENCES

1. Parente Costa L, Bonfá E, Martinago CD, de Oliveira RM, Carvalho JF, Pereira RM. Juvenile onset Systemic Lupus Erythematosus thyroid dysfunction: a subgroup with mild disease? *J Autoimmun* 2009; **33**: 121-124.
2. Sallum AME, Kiss MHB, Sachetti S, *et al.* Juvenile Dermatomyositis: clinical. laboratorial. histological. therapeutical and evolutive parameters of 35 patients. *Arq. Neuropsiquiatr* 2002; **60**: 889-899.
3. Deen ME, Porta G, Fiorot FJ, Campos LM, Sallum AM, Silva CA. Autoimmune hepatitis and juvenile systemic lupus erythematosus. *Lupus* 2009; **18**: 747-751.
4. Montecucco C, Ravelli A, Caporali R, *et al.* Autoantibodies in juvenile dermatomyositis. *Clin Exp Rheumatol* 1990; **8**: 193-196.
5. Martínez-Cordero E, Martínez-Miranda E, Aguilar León DE. Autoantibodies in juvenile dermatomyositis. *Clin Rheumatol* 1993; **12**: 426-428.
6. Go T, Mitsuyoshi I. Juvenile dermatomyositis associated with subclinical hypothyroidism due to auto-immune thyroiditis. *Eur J Pediatr* 2002; **161**: 358-359.
7. Lidar M, Braf A, Givol N, *et al.* Anti-insulin antibodies and the natural autoimmune response in systemic lupus erythematosus. *Lupus* 2001; **10**: 81-86.
8. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis and Rheumatism* 1997; **40**: 1725.
9. Bohan A, Peter JB. Polymiositis and dermatomyositis. *N Engl J Med* 1975; **13**: 344-347.
10. Franklyn JA. Hypothyroidism. *Medicine* 2005; **33**: 27-29.

11. American Diabetes Association. Standards of medical care in diabetes 2007 (Positional Statement). *Diabetes Care* 2007; **30**: S4-S41.
12. Alvarez F, Berg PA, Bianchi FB, *et al.* International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol* 1999; **31**: 929-938.
13. Kaplan MM, Gershwin ME. Primary biliary cirrhosis. *N Engl J Med* 2005; **353**: 1261-1273.
14. De Block CE, De Leeuw IH, Van Gaal LF. Autoimmune gastritis in type 1 diabetes: a clinically oriented review. *J Clin Endocrinol Metab* 2008; **93**: 363-371.
15. Catassi C, Fasano A. Celiac disease diagnosis: simple rules are better than complicated algorithms. *Am J Med* 2010; **123**: 691-693.
16. Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol* 2002; **29**: 288-291.
17. Brunner HI, Silverman ED, To T, Bombardier C, Feldman BM. Risk factors for damage in childhood-onset systemic lupus erythematosus: cumulative disease activity and medication use predict disease damage. *Arthritis Rheum* 2002; **46**: 436-444.
18. Bode RK, Klein-Gitelman MS, Miller ML, Lechman TS, Pachman LM. Disease activity score for children with juvenile dermatomyositis: reliability and validity evidence. *Arthritis Rheum* 2003; **49**: 7-15.
19. Lovell DJ, Lindsley CB, Rennebohm RM, *et al.* Development of validated disease activity and damage indices for the juvenile idiopathic inflammatory myopathies. II. The Childhood Myositis Assessment Scale (CMAS): a quantitative tool for the evaluation of muscle function. The Juvenile Dermatomyositis Disease Activity Collaborative Study Group. *Arthritis Rheum* 1999; **42**: 2213-2219.

20. Ronchezel MV, Len CA, Spinola e Castro A, *et al.* Thyroid function and serum prolactin levels in patients with juvenile systemic lupus erythematosus. *J Pediatr Endocrinol Metab* 2001; **14**: 165-169.

Table 1 – Organ-specific autoantibodies and diseases, and other autoantibodies in juvenile systemic lupus erythematosus (JSLE) *versus* juvenile dermatomyositis (JDM) patients

Variables	JSLE n=41	JDM n=41	p
Organ-specific antibodies	17 (41)	11 (27)	0.24
Autoimmune thyroiditis (anti-TG and/or anti-TPO and/or TRAb)	10 (24)	6 (15)	0.41
Type 1 diabetes mellitus (IAA and/or anti-GAD and/or anti-IA2)	8 (20)	6 (15)	0.77
Celiac disease (EMA)	1 (2)	1 (2)	1.0
Autoimmune hepatitis (SMA and/or anti-LKM-1)	1 (2)	2 (5)	1.0
Primary biliar cirrhosis (AMA)	0 (0)	0 (0)	1.0
Autoimmune gastritis (PCA)	1 (2)	0 (0)	1.0
Organ-specific diseases	4/17 (24)	0/11 (0)	0.13
Other autoantibodies			
ANA	38 (93)	24 (59)	0.0006
RF	4 (10)	0 (0)	0.12
Anti-dsDNA	25 (61)	1 (2)	< 0.0001
Anti-Sm	11 (27)	2 (5)	0.01
Anti-RNP	9 (22)	1 (2)	0.02
Anti-Ro	14 (35)	0 (0)	< 0.0001
Anti-La	6 (15)	0 (0)	0.03
Anti-Scl-70	0 (0)	0 (0)	1.0
Anti-Jo1	0 (0)	2 (5)	0.49
aCL-IgM	20 (49)	17 (41)	0.66
aCL-IgG	19 (46)	5 (12)	0.001
LAC	5 (12)	1 (2)	0.2
p-ANCA	4 (10)	0 (0)	0.12
c-ANCA	1 (2)	1 (2)	1.0

Data are expressed in n (%); anti-TG - anti-thyroglobulin antibody, anti-TPO - anti-thyroid peroxidase antibody, TRAb - anti-thyroid stimulating hormone (TSH) receptor antibody, IAA - insulin autoantibody, anti-GAD - anti-glutamic acid decarboxylase antibody, anti-IA2 - anti-tyrosine phosphatase antibody, EMA - anti-endomysial antibody, SMA - anti-smooth muscle antibody, anti-LKM-1 - anti- type I liver-kidney microsomal antibody, AMA - antimitochondrial antibody, PCA - parietal cell autoantibody, ANA - antinuclear antibody, RF -rheumatoid factor, anti-dsDNA - anti-double-stranded DNA, anti-Scl70 - anti-topoisomerase 1, aCL – anticardiolipin, LAC - lupus anticoagulant, p-ANCA – perinuclear anti-neutrophil cytoplasm antibody, c-ANCA – cytoplasmic anti-neutrophil cytoplasm antibody.

Table 2 – Demographic data, disease activity, treatment and other autoantibodies in juvenile lupus erythematosus (JSLE) and juvenile dermatomyositis (JDM) patients with and without organ-specific autoantibodies

JSLE Variables	JSLE with organ-specific antibody (n=17)	JSLE without organ-specific antibody (n=24)	p
Demographic data			
Female gender	13 (76)	22 (92)	0.21
Current age, years	11 (4-13)	11 (6-17)	0.18
Disease duration, years	3.1 (0.3-7.6)	3.8 (0-12.3)	0.78
SLEDAI-2K	5 (0-12)	3 (0-14)	0.36
SLICC/ACR-DI	1 (0-2)	1 (0-2)	0.93
Current treatment			
Prednisone	14 (83)	23 (96)	0.29
Immunosuppressive use	7 (41)	17 (71)	0.11
Other autoantibodies			
ANA	15 (88)	23 (96)	0.56
anti-dsDNA	11 (65)	14 (58)	0.75
anti-Sm	6 (35)	5 (21)	0.48
anti-RNP	5 (29)	4 (17)	0.45
anti-Ro	8 (47)	6 (25)	0.19
anti-La	3 (18)	3 (13)	0.68
aCL-IgM	10 (59)	11 (46)	1.69
aCL-IgG	7 (41)	12 (50)	0.75
JDM Variables	JDM with organ-specific antibody (n=11)	JDM without organ-specific antibody (n=30)	p
Demographic data			
Female gender	10 (91)	19 (63)	0.13
Current age, years	12 (5-17)	11 (6-18)	0.92
Disease duration, years	3.7 (1.1-8.1)	3.7 (0-13.5)	0.86
JDM scores and muscle enzymes			
CMAS (0 - 52)	50 (44-52)	48.5 (4-52)	0.27
MMT (0 - 80)	80 (75-80)	80 (38-80)	0.47
DAS (0 - 20)	2 (0-7)	3 (0-17)	0.71
AST (10 – 36 UI/L)	23.5 (12-43)	25.5 (14-90)	0.57
ALT (24 – 49 UI/L)	34 (29-103)	33.5 (10-123)	0.76
CPK (39 – 170 UI/L)	93 (26-165)	92.5 (40-27381)	0.72
Aldolase (<7.6 UI/L)	7.05 (3.5-9.4)	7.2 (2.7-49.9)	0.95
LDH (240 – 480 UI/L)	159.5 (135-238)	200 (87-522)	0.19
Current treatment			
Prednisone	6 (55)	15 (50)	1.0
Immunosuppressive use	7 (64)	17 (57)	0.74
Other autoantibodies			
ANA	5 (45)	19 (63)	0.48
aCL-IgM	5 (45)	12 (40)	1.0

Data are expressed in n (%) or median (range), SLEDAI-2K - Systemic Lupus Erythematosus Disease Activity Index 2000, SLICC/ACR-DI- Systemic Lupus International Collaborating Clinics/ACR Damage Index, ANA – antinuclear antibody, anti-dsDNA - anti-double-stranded DNA, aCL – anticardiolipin, CMAS – Childhood Muscle Assessment Score, MMT – Manual Muscle Testing, DAS – Disease Activity Score, AST – aspartate aminotransferase, ALT – alanine aminotransferase, CPK – creatine phosphokinase, LDH – lactate dehydrogenase.

Table 3 – Demographic data, disease activity, other autoantibodies and treatment in four juvenile systemic lupus erythematosus (JSLE) patients with organ-specific autoimmune diseases

Case	1	2	3	4
Demographic data				
Age at JSLE diagnosis, years	11.6	15.6	11.1	9.3
Age at organ-specific autoimmune disease, years	11.4	12	11.6	13.2
Current age, years	15	18.9	16.3	12.6
Gender	female	female	female	female
Organ-specific autoimmune disease	T1DM and HT	T1DM and HT	Subclinical hypothyroidism	Celiac disease
Organ-specific antibodies	Anti-TPO and IAA	TRAb, IAA and Anti-GAD	Anti-TG	EMA
Clinical features at JSLE diagnosis				
Mucocutaneous involvement	-	+	-	+
Arthritis	+	-	+	-
Serositis	+	-	+	+
Hematological abnormalities	-	+	+	-
Neuropsychiatric involvement	-	-	-	-
Nephritis	-	+	+	-
Disease activity and damage at organ-specific antibodies assessment				
SLEDAI-2K	8	8	12	8
SLICC/ACR-DI	2	1	1	0
Current treatment				
JSLE	Prednisone	Prednisone, chloroquine and azathioprine	Prednisone, chloroquine and azathioprine	Prednisone and chloroquine
Organ-specific autoimmune disease	Insulin and levothyroxine supplementation	Insulin and levothyroxine supplementation	-	Gluten-free diet

T1DM - type 1 diabetes mellitus, HT - Hashimoto thyroiditis, Anti-TPO - anti-thyroid peroxidase antibody, IAA - insulin autoantibody, TRAb - anti-thyroid stimulating hormone (TSH) receptor antibody, Anti-GAD - anti-glutamic acid decarboxylase antibody, Anti-TG - anti-thyroglobulin antibody, EMA - anti-endomysial antibody, SLEDAI-2K - Systemic Lupus Erythematosus Disease Activity Index 2000, SLICC/ACR-DI - Systemic Lupus International Collaborating Clinics/ACR (SLICC/ACR) Damage Index, + positive, - negative

Case report

Penile and scrotum swellings in juvenile dermatomyositis

Adriana Maluf Elias Sallum¹, Marco Felipe Castro Silva¹, Cíntia Maria Michelin¹, Ricardo Jordão Duarte², Ronaldo Hueb Baroni³, Nádia Emi Aikawa^{1,4}, Clovis Artur Silva^{1,4}

¹Pediatric Rheumatology Unit, ²Division of Urology, ³Radiology Department and ⁴Division of Rheumatology, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

Correspondence author:

Dr. A. M. E. Sallum

Av Juriti 187, apto 21

São Paulo, SP, Brazil

CEP 04520-000

Phone: 55 11 5051-1621, FAX: 55 11 3214-0032

e-mail: adriana.sallum@icr.usp.br

RESUMO

O edema é uma característica bem conhecida da dermatomiosite juvenil (DMJ). No entanto, para nosso conhecimento, edema simultaneamente localizados no pênis e no escroto não foi relatado. Durante um período de 27 anos, 5.506 pacientes foram acompanhados na Unidade de Reumatologia Pediátrica do nosso Hospital Universitário e 157 pacientes (2,9%) tiveram DMJ. Um deles (0,6%) desenvolveu edema localizado concomitante no pênis e no escroto. Ele apresentava atividade grave da doença, vasculite cutânea difusa, edema localizado recorrente (membros e/ou face) e um episódio de edema generalizado desde os 7 anos de idade. À admissão, ele apresentava há um mês edema proeminente e difuso do pênis e do escroto, indolor e eritema cutâneo leve. A ultra-sonografia peniana, escrotal e testicular mostrou edema cutâneo, sem envolvimento testicular, como também observado na ressonância magnética. Na ocasião, ele fazia uso de prednisona, metotrexato, ciclosporina, hidroxicloroquina e talidomida. Ele recebeu 4 doses semanais de rituximab 375 mg/m² por dose, com melhora das lesões cutâneas e do edema peniano e escrotal. Nenhum evento adverso foi observado após a terapia anti-CD20. Portanto, edema peniano e escroto foi uma manifestação rara da DMJ ativa, com melhora após terapia com anticorpo monoclonal anti-CD20 direcionada contra células B.

PALAVRAS CHAVE: dermatomiosite juvenil, rituximabe, pênis, escroto, edema

ABSTRACT

Edema is a well-known feature of the juvenile dermatomyositis (JDM). However, to our knowledge simultaneously localized penile and scrotum swellings were not reported. During a 27-year period, 5,506 patients were followed up at the Pediatric Rheumatology Unit of our University Hospital and 157 patients (2.9%) had JDM. One of them (0.6%) had concomitant localized penile and scrotum swellings. He had severe disease activity, diffused cutaneous vasculitis, recurrent localized edema (limbs and/or face) and one episode of generalized edema since he was 7 years old. At admission, he had one-month prominent and diffused swellings of the penis and scrotum, painless and mild skin erythema. Penis, scrotum and testicular ultrasound showed skin edema without testicular involvement, as it was observed in the magnetic resonance imaging. On that occasion, he had been taking prednisone, methotrexate, cyclosporin, hydroxychloroquine and thalidomide. He received 4 weekly doses of rituximab at 375 mg/m² per dose with improvements of skin rash, penile and scrotum swellings. No adverse event was observed after anti-CD20 therapy. Therefore, penile and scrotum edema was a rare manifestation of active JDM with improvement after anti-CD20 monoclonal antibody targeting B cells treatment.

KEYWORDS: juvenile dermatomyositis, rituximab, penis, scrotum, edema

INTRODUCTION

Juvenile dermatomyositis (JDM) is a systemic disease characterized by nonsuppurative inflammation of the skeletal muscle and skin^{1,2}. The disease is initially marked by the presence of vasculitis and later on by the development of calcinosis³.

Constitutional symptoms, as fever, alopecia, weight loss, fatigue, headache and irritability, are usually present at the disease onset⁴. Of note, edema is a well-known feature of the disease, particularly in localized areas. The most common regions of this manifestation are eyelids, face and distal extremity regions⁵. Generalized edema associated with JDM was rarely reported⁵⁻⁹. To our knowledge simultaneously localized penile and scrotum swelling in JDM patient were not reported.

During a 27-year period (January 1983 to December 2010), 5,506 patients were followed up at the Pediatric Rheumatology Unit of Instituto da Criança, Faculdade de Medicina da Universidade de São Paulo and 157 patients (2.9%) had JDM. One of our pre-pubertal JDM patients (0.6%) had concomitant localized penile and scrotum swellings without testicular involvement, and was described.

CASE REPORT

A 10-year-old boy was diagnosed with JDM according to Bohan and Peter criteria due to Gottron's papules, heliotrope rash, muscle weakness, increased muscle enzymes serum levels, inflammatory infiltrate and perifascicular atrophy at muscle histopathology and characteristic electromyographic changes¹⁰. He had severe disease activity, diffused cutaneous vasculitis and recurrent localized edema (limbs and/or face) and one episode of generalized edema since he was 7 years old. Remarkably, he has had JDM chronic course and developed calcinosis in numerous sites of the body and considerable limitations at multiple joints, as elbows, wrists, hips, knees and ankles. He was treated with intravenous methylprednisolone, prednisone, methotrexate, cyclosporine, hydroxychloroquine

sulphate, alendronate, diltiazem, thalidomide and intravenous immunoglobulin. At admission at our University Hospital, he had one-month prominent and diffused penile and scrotum swellings, painless and mild skin erythema (Figure 1). An erythematosus rash was also observed in pubic region. At the same moment, he presented periorbital rash, erythematous maculopapular lesions on the extensor surfaces of the hands, vasculitis, photosensitivity, diffused calcinosis, symmetric proximal weakness with a grade-3 muscular strength and significant muscular atrophy. The Childhood Myositis Assessment Scale (CMAS)¹¹ and the Disease Activity Score (DAS)¹² were not performed due to knees imitation. On that occasion, he had been taking prednisone 0.12mg/kg/day, methotrexate 1.0mg/kg/week, cyclosporin 5.0mg/kg/day, hydroxychloroquine 6.2mg/kg/day, alendronate 70mg/week, diltiazem 5.6mg/kg/day and thalidomide 2.3mg/kg/day. Erythrocyte sedimentation rate was 62 mm/h (normal range 0-20 mm/h) and serum muscle enzymes showed aspartate aminotransferase 40 U/l (normal range 10-34 U/l), alanine aminotransferase 32 U/l (normal range 10-44 U/l), creatine kinase 50 U/l (normal range 24-204 U/l), lactic dehydrogenase 272 U/l (normal range 211-423 U/l), aldolase 11.8 U/l (normal range 1-7.5 U/l), albumin 4.3 g/dl (normal range 3.8-5.6 g/dl), urea 13 mg/dl (normal range 15-45 mg/dl) and creatinine 0.16 mg/dl (normal range 0.6-0.9 mg/dl). He was on pre-pubertal stage and the hormone profile was normal: follicle-stimulating hormone - FSH 4.39 IU/l (normal range 1,5-12,4 IU/l), luteinizing hormone – LH 1.09 IU/l (normal range 0,1-7,8 IU/l), and morning total testosterone 0.03 ng/dl (normal range 0,03-0,68 ng/dl). Immunological tests were positive for antinuclear antibodies (ANA) 1:640 (fine speckled pattern) and anti-Ro 52 Kd, and negative for other serum antibodies: anti-Mi-2, anti-synthetase (anti-Jo-1, anti-PL-7 and anti-PL-12), anti-Ku, anti-PM-Scl, anti-double stranded DNA (anti-dsDNA), anti-Sm, anti-RNP, anti-La and anti-Scl-70. Penis, scrotum and testicular ultrasound showed skin edema without testicular involvement, as it was observed in the magnetic resonance imaging. He received 4 weekly doses of rituximab at 375 mg/m² per dose with improvements of skin rash, penile and scrotum swellings (Figure 2). No adverse event was observed after anti-CD20 monoclonal antibody therapy.

DISCUSSION

As far as we are concerned, this is the first case of genitalia edema without orchitis in active JDM patients. Moreover, the prevalence of this manifestation in our teaching pediatric Hospital was rare.

Edema is a clinical feature of this disorder, usually confined to the face or limbs. Anasarca has been rarely described in the beginning and during the disease course⁵⁻⁹, as observed herein. Our recent Brazilian multicenter study, which included 189 JDM patients, showed that facial edema was observed in 34% at the onset disease and body edema in 15%⁴.

Of note, the pathogenesis of edema in JDM is still unknown^{1,2}. This manifestation is supposed to be mediated by an immune complex vasculitis resulting in widespread endothelial injury, membrane attack complex of complement and increased capillary permeability¹³.

Our patient had erythematous, painless and homogeneous penile edema with prepuce involvement. Skin infections, renal dysfunction, hypoalbuminemia and cancer were excluded in our patient, suggesting that penile edema is a disease manifestation of active JDM. A penis carcinoma with tender swelling of the distal penile shaft was evidenced in one adult with dermatomyositis¹⁴. In fact, association between JDM and cancer was observed in 2/189 (1%) of our Brazilian multicenter study, not including penile malignancy⁴.

In addition, other urogenital involvement and gonadal dysfunction associated with JDM were infrequently reported. Dystrophic calcification in ureter area was observed in one of our active JDM patients¹⁵. Jalleh et al evidenced testicular necrotizing vasculitis in a 7-year-old boy suffering from this disease¹⁶, and scrotum and testicular edema with calcinosis were also recently described in two of our JDM patients¹⁷. Moreover, Moraes et al found minor sperm abnormalities in 5 JDM post-pubertal patients¹⁸.

Our patient had a severe disease and was previously treated with various immunosuppressive drugs concomitantly. Interestingly, the genital edema improved only after anti-CD20 monoclonal antibody targeting B cells treatment.

Indeed, rituximab is beneficial for patients with inflammatory myopathies, including JDM, without severe adverse events, as observed herein¹⁹.

In conclusion penile and scrotum edema was a rare manifestation of active JDM with improvement after anti-CD20 monoclonal antibody targeting B cells treatment.

ACKNOWLEDGMENT

This study was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo – FAPESP (grant #08/58238-4), by Conselho Nacional de Desenvolvimento Científico e Tecnológico – CNPQ (grant #300248/2008-3 to CAS) and Federico Foundation grants to CAS.

REFERENCES

1. Sallum AM, Kiss MH, Sachetti S, et al. Juvenile dermatomyositis: clinical, laboratorial, histological, therapeutical and evolutive parameters of 35 patients. *Arq Neuropsiquiatr* 2002;60:889-99.
2. Sallum AM, Kiss MH, Silva CA, et al. MHC class I and II expression in juvenile dermatomyositis skeletal muscle. *Clin Exp Rheumatol* 2009;27:519-26.
3. Feldman BM, Rider LG, Reed AM, Pachman LM. Juvenile dermatomyositis and other idiopathic inflammatory myopathies of childhood. *Lancet* 2008;371:2201-12.
4. Sato JO, Sallum AM, Ferriani VP, et al. A Brazilian registry of juvenile dermatomyositis: onset features and classification of 189 cases. *Clin Exp Rheumatol* 2009;27:1031-8.
5. Saygi S, Alehan F, Baskin E, Bayrakci US, Ulu EMK, Ozbek N. Juvenile dermatomyositis presenting with anasarca. *J Child Neurol* 2008;23:1353-6.
6. Zedan M, El-Ayouty M, Abdel-Hady H, Shouman B, El-Assmy M, Fouda A. Anasarca: not a nephrotic syndrome but dermatomyositis. *Eur J Pediatr* 2008;167:831-4.
7. Mourão AF, Pinto TL, Falcão S, Ribeiro C, Vieira H, Caetano-Lopes J et al. Juvenile dermatomyositis associated with anasarca - a clinical case. *Acta Reumatol Port* 2009;34:276-80.
8. Mehndiratta S, Banerjee P. Juvenile dermatomyositis presenting with anasarca. *Indian Pediatr* 2004;41:752-3.
9. Karabiber H, Aslan M, Alkan A, Yakinci C. A rare complication of generalized edema in juvenile dermatomyositis: a report of one case. *Brain Dev* 2004;26:269-72.
10. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). *N Engl J Med* 1975;292:344-7.

11. Lovell DJ, Lindslev CB, Rennebohm RM, et al. Development of validated disease activity and damage indices for the juvenile idiopathic inflammatory myopathies. II. The Childhood Myositis Assessment Scale (CMAS): a quantitative tool for the evaluation of muscle function. The Juvenile Dermatomyositis Disease Activity Collaborative Study Group. *Arthritis Rheum* 1999;42:2213-2219
12. Bode RK, Klein-Gitelman MS, Miller ML, Lechman TS, Pachman LM. Disease activity score for children with juvenile dermatomyositis: reliability and validity evidence. *Arthritis Rheum* 2003;49:7-15.
13. Gonçalves FG, Chimelli L, Sallum AM, Marie SK, Kiss MH, Ferriani VP. Immunohistological analysis of CD59 and membrane attack complex of complement in muscle in juvenile dermatomyositis. *J Rheumatol* 2002;29:1301-7.
14. Lalla SC, Aldridge RD, Tidman MJ. Carcinoma of the penis presenting with dermatomyositis. *Clin Exp Dermatol* 2001;266:558.
15. Duarte RJ, Denes FT, Sallum AM. Ureteral calcinosis in juvenile dermatomyositis: successful precocious surgical management. *Int Braz J Urol* 2006;32:574-7.
16. Jalleh RP, Swift RI, Sundaresan M, Toma A, Wood CB. Necrotising testicular vasculitis associated with dermatomyositis. *Br J Urol* 1990;66:660.
17. Sallum AM, Garcia AJ, Saito OC, Silva CA. Scrotum and testicular calcinosis in juvenile dermatomyositis (JDM). A report of two cases. *Clin Exp Rheumatol* 2009;27:382-3.
18. Moraes AJ, Pereira RM, Cocuzza M, Casemiro R, Saito O, Silva CA. Minor sperm abnormalities in young male post-pubertal patients with juvenile dermatomyositis. *Braz J Med Biol Res* 2008;41:1142-7.
19. Tzaribachev N, Koetter I, Kuemmerle-Deschner JB, Schedel J. Rituximab for the treatment of refractory pediatric autoimmune diseases: a case series. *Cases J* 2009;2:6609.

Figure 1 - Penile and scrotum swellings in one juvenile dermatomyositis patient

Figure 2 – Improvements penile and scrotum swellings after rituximab therapy in one juvenile dermatomyositis patient

Menstrual and hormonal alterations in juvenile dermatomyositis

N.E. Aikawa^{1,2}, A.M.E. Sallum¹, M.M. Leal³, E. Bonfá², R.M.R. Pereira², C.A.A. Silva^{1,2}

¹Paediatric Rheumatology Unit, ²Rheumatology Division, and ³Adolescent Unit, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

Abstract

Objective

To evaluate age at menarche, menstrual cycles and hormone profile in juvenile dermatomyositis (JDM) patients and controls.

Methods

Twelve consecutive JDM patients were compared to 24 age-matched healthy subjects. Age at menarche and age of maternal menarche were recorded. Menstrual cycle was evaluated prospectively for 6 consecutive months and the mean cycle length and flow were calculated. The hormone profile was collected on the last menstrual cycle. Demographic data, clinical features, muscle enzymes, JDM scores and treatment were analysed.

Results

The median of current age of JDM patients and controls was similar (18 vs. 17 years, $p=0.99$). The median age at menarche of the JDM patients was higher than in the control group (13 vs. 11 years, $p=0.02$) whereas the median age of maternal menarche was alike in both groups (12 vs. 13 years, $p=0.67$). Menstrual disturbances were not observed, except for one patient who had longer length of menstrual cycle. The median of follicle stimulating hormone (FSH) was significantly higher in JDM patients compared to controls (4.5 vs. 3.0 IU/L, $p=0.02$) and none of them had premature ovarian failure (POF). The median of progesterone was significantly lower in JDM patients (0.3 vs. 0.7 ng/mL, $p=0.01$) with a higher frequency of decreased progesterone compared to controls (75% vs. 29%, $p=0.01$).

Conclusions

Our study identifies in JDM patients delayed menarche with normal cycles and low follicular reserve. The decreased progesterone levels may suggest an underlying subclinical corpus luteum dysfunction in this disease.

Key words

Juvenile dermatomyositis, menstrual abnormalities, menarche, hormone

Nádia E. Aikawa, MD, PhD
 Adriana M.E. Sallum, MD, PhD
 Marta M. Leal, MD, PhD
 Eloísa Bonfá, MD, PhD
 Rosa M.R. Pereira, MD, PhD
 Clovis A.A. Silva, MD, PhD

This study was sponsored by the Conselho Nacional de Desenvolvimento Científico e Tecnológico – CNPQ (grants 305468/2006-5 to Dr Bonfá, 300559/2009-7 to Dr Pereira, Edital MCT/ CNPq 472953/2008-7 and 300248/2008-3 to Dr Silva) and Federico Foundation Grant to Dr Bonfá, Dr Pereira and Dr Silva.

Please address correspondence and reprint requests to:

Clovis Artur A. Silva
 Rua Araiões, 152/81,
 Vila Madalena,
 São Paulo,
 CEP 05442-010, Brazil.

E-mail: clovis.silva@icr.usp.br

Received on July 11, 2009; accepted in revised form on January 11, 2010.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2010.

Introduction

We have previously shown delayed menarche and a high frequency of menstrual and hormone alterations in juvenile systemic lupus erythematosus (JSLE) patients compared to controls (1-3). However, no study has prospectively evaluated menstrual cycle and hormonal status of juvenile dermatomyositis (JDM) patients. We have therefore performed a detailed evaluation of age at menarche, menstrual disturbances and hormonal profile in JDM patients and compared them with healthy adolescents.

Materials and methods

Twelve consecutive JDM female patients from the Paediatric Rheumatology Unit or the Rheumatology Division of University of São Paulo were evaluated. All patients fulfilled the Bohan and Peter criteria for JDM (4). The control group included 24 healthy female adolescents followed at the educational and preventive Adolescent Unit at our University Hospital. None of them had current pregnancy or was under hormonal contraceptive agents. The Brazilian socio-economic classes were classified according to Associação Brasileira dos Institutos de Pesquisa de Mercados (5). This study was approved by the local Ethics Committee and informed consent was obtained from all participants. Ages at menarche were registered based on recollection of JDM patients and controls, and their respective mothers. The age at menarche of the mother was also systematically recorded. Menstrual cycle was evaluated prospectively for 6 consecutive months and the mean cycle length and flow were calculated. Normal cycle was defined as length varying from 25 to 35 days with 3 to 7 days of duration of blood flow (1, 3). Menstrual disturbances were based on alterations in one or more of these parameters during evaluation. Amenorrhea and sustained amenorrhea were defined as the cessation of menstruation for more than 4 months after menarche and persisting for more than 12 months, respectively. Patients with sustained amenorrhea in whom menstruation did not resume and with follicle-stimulating hormone (FSH) levels >40 IU/L fulfilled the diagnosis

of premature ovarian failure (POF) (6). Secondary sexual characteristics were classified according to pubertal changes (7). Body mass index (BMI) was defined by the formula: BMI (kg/m²) weight in kilograms/height in square-metres.

Hormonal determinations were performed for all JDM patients and controls at the last evaluated menstrual cycle or randomly for those with amenorrhea. Serum levels of FSH, luteinizing hormone (LH), estradiol, prolactin, progesterone and total testosterone were measured by fluoroimmunoassay using kits from DELPHIA^R time-resolved fluoroimmunoassay (WALLAC Ou, Turku, Finland) on days 1, 2 or 3 of the menstrual cycle (or randomly for those with amenorrhea) according to pubertal changes (7) and age. Intra and inter-assay coefficients of variation recommended by the manufacturer were limited to 3.5% and 2.1%, respectively.

Clinical manifestations of JDM were defined as cutaneous lesions (heliotrope, Gottron's papules, vasculitis, calcinosis, ulcerative skin or malar rash), articular involvement (nonerosive arthritis), muscular involvement (muscle weakness), cardiopulmonary disease (serositis, myocarditis, restrictive lung disease or pulmonary hypertension) and gastrointestinal involvement (dysphagia or vasculitis). Disease activity was assessed at menarche, at diagnosis and at study entry by using disease activity score (DAS) (8), childhood myositis assessment scale (CMAS) (9) and manual muscle testing (MMT) (10). Data concerning the current dosage of prednisone, and the use of methotrexate, azathioprine, chloroquine and cyclosporine were determined at diagnosis and at study entry. In addition, cumulative doses of prednisone and disease duration until the first period were evaluated.

Statistical analysis

Results were presented as the median (range) for continuous variables and number (%) for categorical variables. Continuous variables were compared using the Mann Whitney test to evaluate differences between JDM patients and control group. For categorical variables differences were assessed by Fisher's

Competing interests: none declared.

Table I. Demographic features, BMI, pattern of pubertal changes and menstrual cycle in JDM patients and controls.

Variables	JDM patients (n=12)	Controls (n=24)	p-value
<i>Demographic features and socio-economic status</i>			
Current age, years	18 (11–20)	17 (13–21)	0.99
Number of school years	10.5 (5–11)	10.5 (8–13)	0.32
Brazilian socio-economic class, C or D	9 (75)	16 (67)	0.71
Occupation	1 (8)	4 (17)	0.64
BMI, kg/m ²	22.1 (17.8–30)	21.1 (15–27.2)	0.36
Adult pubertal status (Tanner 4 or 5)	9 (75)	19 (79)	1.0
<i>Menarche and menstrual cycle</i>			
Age at menarche, years	13 (10–15)	11 (9–14)	0.02
Age at maternal menarche, years	12 (11–17)	13 (10–16)	0.67
Gynaecological age*, years	4 (1–8)	6 (2–10)	0.11
Menstrual disturbances	1 (8)	2 (8)	1.0
Flow duration, days	5 (3–6)	5 (3–8)	0.13
<3	0 (0)	0 (0)	1.0
>7	0 (0)	1 (4)	1.0
Length of cycle, days	28 (27–75)	30 (24–35)	0.14
<25	0 (0)	1 (4)	1.0
>35	1 (8)	0 (0)	0.33
Amenorrhea frequency	0 (0)	0 (0)	1.0

Values expressed in n (%) or median (range). JDM: juvenile dermatomyositis; BMI: body mass index; *time between menarche and current age.

exact test. Pearson's coefficient was used to evaluate correlations between age at menarche in JDM patients and cumulative doses of prednisone, disease duration and JDM scores until the first period. In all statistical tests significance was set at a *p*-value <0.05.

Results

Demographic features and BMI

The distribution of demographic features revealed that JDM patients and controls were comparable regarding median current age (18 vs. 17 years, *p*=0.99), number of school years (10.5 vs. 10.5, *p*=0.32), frequency of the two lowest Brazilian socio-economic classes (C or D) (75% x 67%, *p*=0.71), occupation (8% vs. 17%, *p*=0.64) and BMI (22.6 vs. 21.1 kg/m², *p*=0.22) (Table I). Median age at JDM onset was 10.1 (3–16) years and median of disease duration was 8.2 (3–11.2) years.

Age at menarche and menstrual cycles

The median age at menarche of JDM patients was higher than in control group (13 vs. 11 years, *p*=0.02) whereas the median maternal age at menarche of JDM patients was similar

to controls (12 vs. 13 years, *p*=0.67). The gynaecological age (time between menarche and current age) was also comparable (*p*=0.11) (Table I). Menarche occurred after JDM onset in 10 patients and before JDM onset in 2. In the former group, no correlation was found between glucocorticoid cumulative doses (until the first period) and menarche age (*p*=0.887) and between disease duration (until the first menstruation) and menarche age (*p*=0.698). Moreover, no correlation was found between muscle enzymes levels (at the first period) and menarche age (CPK, *p*=0.672; ALT, *p*=0.262; AST, *p*=0.502; aldolase, *p*=0.335; LDH, *p*=0.887) or JDM scores (at the first menstruation) and menarche age (DAS, *p*=0.342; CMAS, *p*=0.142; MMT, *p*=0.091).

The secondary sexual characteristics according to pattern of pubertal changes (7) were similar in JDM and controls, particularly Tanner 4 and 5 (75% vs. 79%, *p*=1.0). The frequency of menstrual alterations in JDM patients (8%) was similar to controls (8%) (*p*=1.0). Accordingly, the frequencies of menstrual abnormalities were comparable in both groups: flow

duration [decreased (<3 days, *p*=1.0) or increased (>7 days, *p*=1.0)] and length of menstrual cycle [shorter (<25 days, *p*=1.0) or longer (>35 days, *p*=0.33)]. The median time of flow duration and length of cycle were also similar [5 (3–6) vs. 5 (3–8) days, *p*=0.13; 28 (27–75) vs. 30 (24–35) days, *p*=0.14] (Table I). None of JDM patients and controls had amenorrhea or POF.

Hormonal profile

The median level of FSH was significantly higher in JDM patients compared to controls [4.5 (2.0–8.8) vs. 3.0 (0.5–16.7) IU/L, *p*=0.02] whereas the frequency of elevated levels of FSH was comparable (*p*=1.0). The median of prolactin was lower in JDM patients than in controls [5.9 (1.7–9.4) vs. 8.9 (5.3–15.2) ng/mL, *p*=0.005], although both were within normal range. The median of progesterone was significantly lower in JDM patients versus controls [0.3 (0.3–4.2) vs. 0.7 (0.3–17.2) ng/mL, *p*=0.01] with a higher frequency of decreased progesterone compared to controls (75% vs. 29%, *p*=0.01). The median and frequencies of altered LH, estradiol and testosterone were comparable in both studied groups (Table II).

Demographic data, clinical features, muscle enzymes levels, JDM scores, hormone profiles and treatment of 12 JDM patients

The median age at disease onset was 10 (3–16) years, all of them with muscle enzymes above the upper normal limit. At diagnosis, seven patients had gastrointestinal symptom, two of them concomitantly with cardiac involvement. The evaluation at study entry revealed that none of them had JDM lipoatrophy with a median time of disease duration of 8.2 (2.3–11.2) years. At time of study entry, nine patients had low progesterone, only three of them were under glucocorticoid therapy. One JDM patient (Case 7) had decreased progesterone with increased menstrual cycle length. All other 11 patients had normal cycles (Table III).

Discussion

To our knowledge, this is the first study that evaluated menstrual cycle con-

comitantly to the hormonal evaluation in adolescents and young JDM patients compared to a healthy control population. We identified delayed menarche with normal cycles and low follicular reserve in JDM. The study also demonstrated a high prevalence of low progesterone in this disease without an association with menstrual abnormalities. The great advantage of this study is prospective design which allows a more accurate definition of menstrual disturbances in adolescent population. In addition, the median gynaecological age over 4 years in both groups excludes menstrual abnormalities due to a physiologic phenomenon of puberty which has been described for the normal adolescent particularly in the first 24 months following the first period (1). In this study, menarche age was recorded by subject's recollection, as previously described in our JSLE population (1-3).

Table II. Hormonal profiles of patients with juvenile dermatomyositis (JDM) versus controls.

Hormones	JDM patients (n=12)	Controls (n=24)	p-value
<i>FSH, UI/L</i>			
Median (range)	4.5 (2–8.8)	3.0 (0.5–16.7)	0.02
Elevated levels, n (%)	1 (8)	2 (8)	1.0
<i>LH, UI/L</i>			
Median (range)	4.1 (2.1–7.3)	2.6 (0.5–71.5)	0.29
Elevated levels, n (%)	1 (8)	5 (21)	0.64
<i>Estradiol, pg/ml</i>			
Median (range)	38 (29–93)	51.7 (17–374)	0.13
Decreased levels, n (%)	0 (0)	1 (4)	1.0
<i>Prolactin, ng/ml</i>			
Median (range)	5.9 (1.7–9.4)	8.9 (5.3–15.2)	0.005
Elevated levels, n (%)	0 (0)	0 (0)	1.0
<i>Progesterone, ng/ml</i>			
Median (range)	0.3 (0.3–4.2)	0.7 (0.3–17.2)	0.01
Decreased levels, n (%)	9 (75)	7 (29)	0.01
<i>Testosterone, ng/dl</i>			
Median (range)	22 (11–75)	33 (1.2–134)	0.47
Elevated levels, n (%)	0 (0)	1 (4)	1.0

JDM: juvenile dermatomyositis; FSH: follicle stimulating hormone; LH: luteinizing hormone.

Table III. Demographic data, clinical features, muscle enzymes, scores, treatment and hormonal profile of 12 patients with juvenile dermatomyositis (JDM) at hormonal evaluation.

Patients	1	2	3	4	5	6	7	8	9	10	11	12
<i>Demographic data</i>												
Disease duration, years	5.0	11.2	3.7	3.0	8.1	8.4	2.3	8.5	8.3	9.7	9.3	7.2
Current age, years	11.2	14.2	14	14.8	15.1	17.5	18.3	17.5	18.4	19.7	19.3	20.2
<i>Clinical features</i>												
Cutaneous	–	+	+	+	–	–	–	–	–	–	–	+
Muscle	–	+	–	–	–	–	+	–	–	–	–	–
Articular	–	–	–	–	–	–	–	–	–	–	–	–
Cardiopulmonary	–	–	–	–	–	–	–	–	–	–	–	–
Gastrointestinal	–	–	–	–	–	–	–	–	–	–	–	–
<i>Muscle enzymes</i>												
CPK (39–308 IU/L)	55	602	96	158	96	70	657	109	33	87	77	125
ALT (24–49 IU/L)	14	60	19	26	20	22	23	22	13	17	18	10
AST (10–36 IU/L)	31	70	34	38	32	27	40	34	22	21	31	22
Aldolase (<7.6 IU/L)	6.7	17.2	5.9	7.3	5.8	4.0	8.1	3.5	3.4	2.8	5.0	3.2
LDH (240–480 IU/L)	137	305	129	168	158	102	203	135	107	336	96	385
<i>Scores</i>												
DAS (0–20)	0	5	3	3	0	0	12	0	0	0	0	6
CMAS (0–52)	52	44	51	52	52	52	51	52	52	52	52	52
MMT (0–80)	80	80	80	80	80	80	76	80	80	80	80	80
<i>Treatment (previous use/current dose, mg)</i>												
Prednisone	+/0	+/5	+/0	+/0	+/0	+/0	+/20	+/0	+/0	+/0	+/0	+/2.5
Cyclosporine	–	–	–	–	–	–	+/200	–	–	–	–	–
Methotrexate	–	+/50	–	+/25	–	–	+/30	–	–	+/0	–	–
Azathioprine	–	–	–	–	–	–	+/100	–	–	–	–	+/150
Chloroquine phosphate	–	+/250	–	–	–	–	–	–	–	+/0	–	+/250
<i>Hormones</i>												
Elevated FSH or LH	–	–	–	–	–	+	–	–	–	+	–	–
Low progesterone	–	+	+	+	–	+	+	+	+	+	–	+
Menstrual disturbance	–	–	–	–	–	–	+	–	–	–	–	–

+ positive; – negative; CPK: creatine phosphokinase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; DHL: lactate dehydrogenase; DAS: Disease Activity Score; CMAS: childhood muscle assessment score; MMT: manual muscle testing; FSH: follicle stimulating hormone; LH: luteinizing hormone.

This data is considered reliable, since menarche is a historical moment in the women's life and remembered over 30 years after its occurrence (11). A possible weakness of our study is the small number of JDM patients, especially with menarche after disease onset.

We previously showed a late occurrence of the first period in JSLE compared with normal Brazilian adolescents (1-3), as observed herein in JDM patients. No clear etiology for the delay of menarche was determined but it is not attributed to the genetic background given that the menarche age of their mothers was similar in groups.

On the other hand, we have reported that adolescent JSLE patients have a remarkable high frequency of menstrual irregularities particularly with longer length of cycles not associated with disease activity or cyclophosphamide treatment (3). In contrast, only one JDM patient of the present study had menstrual alteration but disease activity does not seem to account for this finding since four other patients had cutaneous activity at study entry without menstrual irregularities.

Regardless of this almost uniform normal cycle, the majority of patients had inadequate or lower production of progesterone in early follicular phase of menstrual cycle as also reported for adults SLE (12) and JSLE (1, 3) suggesting a possible luteal dysfunction (13, 14) in this disease. In fact, a high frequency of decreased progesterone level and normal LH was observed in lupus patients with normal cycles (3). We are currently investigating the possible role of anti-corpus luteum antibodies in JDM population. Moreover, glucocorticoid may act directly on the hypothalamic-pituitary-ovarian axis and reduce gonadotropin-releasing hormone (GnRH) pulse frequency and pituitary LH and FSH secretion, as well as pro-

gesterone levels (15). This factor does not seem to be relevant in JDM since most patients with low progesterone levels were not under this therapy.

Of interest, FSH levels in JDM patients were within normal range but significantly higher than in controls, indicating a reduced ovarian reserve not explained by distinct patterns of puberty, as also observed in adolescent SLE patients (3). FSH increases throughout the reproductive years (16) and it is the most sensitive marker of ovarian function (6). Reinforcing this notion, we have demonstrated that this hormone was a marker for severe sperm abnormalities in male lupus population (17).

In spite of the small number of patients and the low disease severity diversity, we have identified in JDM patients delayed menarche with normal cycles and low follicular reserve. The decreased progesterone levels may suggest an underlying subclinical corpus luteum dysfunction in this disease. Larger prospective studies are essential to confirm the present data.

Acknowledgements

Our thanks go to Dr. Ulysses Dória Filho for the statistical analyses and Prof. Thelma Suely Okay for the hormonal evaluation.

References

1. SILVA CA, LEAL MM, LEONE C *et al.*: Gonadal function in adolescents and young female with systemic lupus erythematosus. *Lupus* 2002; 11: 419-25.
2. FEBRONIO MV, PEREIRA RM, BONFA E, TAKIUTI AD, PEREYRA EA, SILVA CA: Inflammatory cervicovaginal cytology is associated with disease activity in juvenile systemic lupus erythematosus. *Lupus* 2007; 16: 430-5.
3. MEDEIROS PB, FEBRÔNIO MV, BONFÁ E, BORBA EF, TAKIUTI AD, SILVA CA: Menstrual and hormonal alterations in juvenile systemic lupus erythematosus. *Lupus* 2009; 18: 38-43.
4. BOHAN A, PETER JB: Polymyositis and dermatomyositis. *N Engl J Med* 1975; 13: 344-7.
5. ALMEIDA PM, WICKERRHAUSER H: Critério

de classe econômica da Associação Brasileira de Anunciantes (ABA) e Associação Brasileira dos Institutos de Pesquisa de Mercado (ABIPME) 1991, pp. 1-29.

6. SILVA CA, BRUNNER HI: Gonadal functioning and preservation of reproductive fitness with juvenile systemic lupus erythematosus. *Lupus* 2007; 16: 593-9.
7. MARSHALL JC, TANNER JM: Variations in patterns of pubertal changes in boys and girls. *Arch Dis Child* 1970; 45: 13-23.
8. BODE RK, KLEIN-GITELMAN MS, MILLER ML, LECHMAN TS, PACHMAN LM: Disease activity score for children with juvenile dermatomyositis: reliability and validity evidence. *Arthritis Rheum* 2003; 49: 7-15.
9. LOVELL DJ, LINDSLEV CB, RENNEBOHM RM *et al.*: Development of validated disease activity and damage indices for the juvenile idiopathic inflammatory myopathies. II. The Childhood Myositis Assessment Scale (CMAS): a quantitative tool for the evaluation of muscle function. The Juvenile Dermatomyositis Disease Activity Collaborative Study Group. *Arthritis Rheum* 1999; 42: 2213-9.
10. LEGG AT, MERRILL JB: Physical therapy in infantile paralysis. In: Principles and practice of physical therapy. Hagerstown, Mock Pemberton and Coulter, 1932.
11. DAMON A, BAJEMA CJ: Age at menarche: Accuracy of recall after thirty-nine years. *Hum Biol* 1974; 46: 381-4.
12. VOGL D, FALK W, DORNER M, SCHÖLMERICH J, STRAUB RH: Serum levels of pregnenolone and 17-hydroxypregnenolone in patients with rheumatoid arthritis and systemic lupus erythematosus: relation to other adrenal hormones. *J Rheumatol* 2003; 30: 269-75.
13. ARNALICH F, BENITO-URBINA S, GONZALEZ-GANCEDO P, IGLESIAS E, DE MIGUEL E, GIJON-BAÑOS J: Inadequate production of the progesterone in women with systemic lupus erythematosus. *Br J Rheumatol* 1992; 31: 247-51.
14. BENITO URBINA S, HARTE LE, GIJON BJ, ARNALICH FF: Hormonal changes in fertile women with quiescent systemic lupus erythematosus. *An Med Interna* 1995; 12: 221-4.
15. SAKETOS M, SHARMAN N, SANTORO NF: Suppression of the hypothalamic-pituitary-ovarian axis in normal women by glucocorticoids. *Biol Reprod* 1993; 49: 1270-6.
16. DE MEDEIROS SF, ASSI PE, DE MEDEIROS MM: Gonadotrophin dynamics during reproductive life. *Int J Gynaecol Obstet* 2004; 87: 24-8.
17. SOARES PM, BORBA EF, BONFA E, HALLAK J, CORRÊA AL, SILVA CA: Gonad evaluation in male systemic lupus erythematosus. *Arthritis Rheum* 2007; 56: 2352-61.

Risk factors associated with calcinosis of juvenile dermatomyositis

Adriana M. E. Sallum,¹ Francine C. M. M. Pivato,² Ulysses Doria-Filho,³
Nádia E. Aikawa,⁴ Bernadete L. Liphaus,⁵ Suely K. N. Marie,⁶ Clovis A. A. Silva⁷

Abstract

Objective: To identify risk factors associated with calcinosis in children and adolescents with juvenile dermatomyositis.

Methods: A review was carried out of the medical records of 54 patients with juvenile dermatomyositis. Data were collected on demographic characteristics, clinical features: muscle strength (stages I to V of the Medical Research Council scale), pulmonary involvement (restrictive pulmonary disease with presence or absence of anti-Jo1 antibodies), gastrointestinal problems (gastroesophageal reflux) and/or heart disease (pericarditis and/or myocarditis); laboratory tests: elevated muscle enzyme levels in serum (creatine phosphokinase, aspartate aminotransferase, alanine aminotransferase and/or lactate dehydrogenase); and on the treatments given: corticoid therapy in isolation or associated with hydroxychloroquine and/or immunosuppressants. The patients were divided into two groups, depending on presence or absence of calcinosis and data were evaluated by both univariate and multivariate analyses.

Results: Calcinosis was identified in 23 (43%) patients, and in six (26%) patients it had emerged prior to diagnosis while in 17 (74%) it was post diagnosis. The univariate analysis revealed that cardiac ($p = 0.01$) and pulmonary ($p = 0.02$) involvement and the need for one or more immunosuppressor (methotrexate, cyclosporine A and/or pulse therapy with intravenous cyclophosphamide) to treat juvenile dermatomyositis ($p = 0.03$) were all associated with an increased incidence of calcinosis. The multivariate analysis then demonstrated that only cardiac involvement (OR = 15.56; 95%CI 1.59-152.2) and the use of one or more immunosuppressor (OR = 4.01; 95%CI 1.08-14.87) were independently associated with the presence of calcinosis.

Conclusions: Calcinosis was a frequent development among these juvenile dermatomyositis cases, generally emerging as the disease progressed. Calcinosis was associated with the more severe cases that also had cardiac involvement and where immunosuppressors had to be included in the treatment.

J Pediatr (Rio J). 2008;84(1):68-74: Juvenile dermatomyositis, calcinosis, risk factors, heart, lungs, immunosuppressors.

Introduction

Juvenile dermatomyositis (JDM) is a multisystemic disease of unknown etiology, which is characterized by vasculitis primarily affecting the skin and muscles.¹⁻³ It is part of a

heterogenous group of acquired muscle diseases, the idiopathic inflammatory myopathies, whose common denominator is the presence of weak muscles with inflammatory infiltrates. Characterization of this group of pathologies is

1. Professora colaboradora, Departamento de Pediatria, Faculdade de Medicina, Universidade de São Paulo (USP), São Paulo, SP, Brazil. Doutora, Faculdade de Medicina, USP, São Paulo, SP, Brazil. Médica assistente, Unidade de Reumatologia Pediátrica, Instituto da Criança – Hospital das Clínicas (ICr-HC), Faculdade de Medicina, USP, São Paulo, SP, Brazil.
2. Médica. Complementação Especializada, Unidade de Reumatologia Pediátrica, ICr-HC, Faculdade de Medicina, USP, São Paulo, SP, Brazil.
3. Doutor. Faculdade de Medicina, USP, São Paulo, SP, Brazil. Núcleo de Consultoria e Apoio, Metodologia de Pesquisa e Estatística (NuCAMPE), Departamento de Pediatria, Faculdade de Medicina, USP, São Paulo, SP, Brazil.
4. Médica. Complementação Especializada, Unidade de Reumatologia Pediátrica, ICr-HC, Faculdade de Medicina, USP, São Paulo, SP, Brazil.
5. Doutora. Faculdade de Medicina, USP, São Paulo, SP, Brazil. Professora colaboradora, Departamento de Pediatria, Faculdade de Medicina, USP, São Paulo, SP, Brazil. Médica assistente, Unidade de Reumatologia Pediátrica, ICr-HC, Faculdade de Medicina, USP, São Paulo, SP, Brazil.
6. Professora associada e livre-docente, Departamento de Neurologia, Faculdade de Medicina, USP, São Paulo, SP, Brazil.
7. Professor livre-docente, Departamento de Pediatria, Faculdade de Medicina, USP, São Paulo, SP, Brazil. Responsável, Unidade de Reumatologia Pediátrica, ICr-HC, Faculdade de Medicina, USP, São Paulo, SP, Brazil.

No conflicts of interest declared concerning the publication of this article.

Suggested citation: Sallum AM, Pivato FC, Doria-Filho U, Aikawa NE, Liphaus BL, Marie SK, et al. Risk factors associated with calcinosis of juvenile dermatomyositis. *J Pediatr (Rio J)*. 2008;84(1):68-74.

Manuscript received Aug 01 2007, accepted for publication Oct 17 2007.

doi:10.2223/JPED.1746

based on its pattern of muscle involvement, the presence of associated clinical manifestations, histopathological findings, response to treatment and prognosis.⁴⁻⁶

This is a rare disease that predominantly affects females, at a proportion of 2:1, and which has an incidence of 3.2/1,000,000 children and adolescents/year in the United States.⁷ Despite its rarity, it is the fourth most frequent disease at tertiary pediatric rheumatology services, and there are no Brazilian studies of its epidemiology.⁸

The initial phase of the disease is characterized by vasculitis⁹ and, later, calcinosis or dystrophic calcifications may appear.¹ These are calcium deposits that appear in muscle or subcutaneous tissues. Patients with calcinosis have normal levels of calcium and phosphorous in serum, in contrast with metastatic calcifications (which are observed with hyperparathyroidism), when these metabolites are at elevated levels.¹⁰

Calcinosis are more common in the pediatric age group, affecting from 10 to 70% of children and adolescents with JDM, compared with 30% of adults with dermatomyositis (DM).^{8,11,12} The etiopathogenesis of calcinosis is unknown. It is believed that calcium salt deposits occur with severe cases of the disease with persistent inflammation¹³ (generalized cutaneous vasculitis, muscle weakness and sustained muscle enzyme levels in elevation) and which do not respond to corticoid therapy.^{8,10,12-16} However, the majority of publications are just case reports.

There is just a single study of 35 cases that has investigated the risk factors associated with calcinosis in patients with JDM, with univariate and multivariate analysis models.¹⁷ The rarity of research into calcinosis in JDM and the significant number of patients with this disease at our service prompted us to carry out this study.

Our objective was, therefore, to investigate risk factors (demographic data, initial and progressive clinical manifestations, laboratory tests and treatment) associated with calcinosis in children and adolescents with JDM.

Methods

This was a cross-sectional study. A total of 54 children and adolescents were studied, enrolled from those treated at the Pediatric Rheumatology Unit of the Instituto da Criança, Hospital das Clínicas, Universidade de São Paulo Medical Faculty (ICr-HC-FMUSP) with diagnoses of JDM. These patients were followed from January 1987 to December 2003. Their definitive diagnoses of JDM were established according to criteria laid out by Bohan & Peter, and recommended by the American College of Rheumatology,⁹ and based on the presence of characteristic erythema associated with three of the four criteria listed in Table 1.

Patients were only enrolled if all of the data described were on their medical records. These patients were followed for a minimum period of 6 months and a maximum of 16 years (mean follow-up period of 5.4 years and median of 6.7 years).

The analysis was retrospective and carried out by means of completing a protocol that covered patients' clinical, laboratory and treatment characteristics. The protocols were then divided into two groups, depending in the presence or absence of calcinosis.

Calcinosis was diagnosed based on the presence of calcium deposits that were palpable on physical examination and/or deposits visible on X-rays of soft tissues and involving the trunk, abdomen, upper and/or lower limbs. These were then classified into four subtypes: calcinosis cutis circumscripta (superficial plaques or nodules confined to the skin or subcutaneous tissue), calcinosis tumoral or *universalis* (large deposits that may extend to deeper tissues, including muscles), calcinosis along the muscular fascia and tendons and extensive calcium deposits all over the surface of the body.¹⁸ All cases had normal levels of calcium and phosphorous in serum.

The two groups were compared in terms of the following characteristics: demographic data (sex, age at disease onset, time between onset of the disease and start of treatment) and

Table 1 - Bohan & Peter's criteria for the diagnosis of juvenile dermatomyositis

---

Cutaneous involvement: violaceous discoloration and edema around the eyes (the heliotrope sign) and/or erythematous scaly papules on the eruption on the knuckles (the Gottron rash)
Symmetrical, muscle weakness at the waist, pelvis and anterior neck flexor muscles, with or without dysphagia and involvement of the respiratory musculature
Elevated muscle enzyme levels, particularly creatine phosphokinase, and frequently aldolase, aspartate aminotransferase, aspartate alanine transferase and lactate dehydrogenase
Electromyography findings show short motor units, polyphase waves, fibrillations, positive waves, insertional irritability, high frequency and repetitive discharges
Muscle biopsy shows evidence of inflammatory myopathy: necrosis of type I and II muscle fibers, phagocytosis, degeneration and regeneration of muscle fibers with variable fiber caliber, interstitial mononuclear cells, endomysial cells, perimysial cells or perivascular cells

---

degree of muscle strength at diagnosis (waist, pelvis and anterior neck flexors, according to Medical Research Council criteria. The latter classification consists of the following stages: 0 (no contraction), 1 (minimal contraction), 2 (active movement in the absence of gravity), 3 (movement against gravity), 4 (movement against gravity and resistance) and 5 (normal strength).¹⁹ Comparisons were also made based on, elevated levels of one or more muscle enzymes (any figure above the upper limit of normality): creatine phosphokinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH). The following characteristics observed during follow-up were also analyzed: pulmonary involvement (presence of restrictive disorders on pulmonary function test and/or interstitial abnormalities on thin slice computerized tomography, with anti-Jo-1 antibody assay), gastrointestinal symptoms (gastroesophageal reflux, assessed by contrastive X-rays of the esophagus, stomach and duodenum and/or pH-metry) and cardiac involvement (pericarditis and/or myocarditis, detected using echocardiogram with Doppler), deaths and their causes and treatment.

All patients were initially treated with prednisone (1 to 2 mg/kg/day) or pulse therapy with methylprednisolone (30 mg/kg/dose for 3 consecutive days). Those who did not respond or who responded partially to corticoid therapy (continued muscle weakness and/or cutaneous activity), were given an antimalarial in association (chloroquine diphosphate or hydroxychloroquine sulphate), immunosuppressors (methotrexate, cyclosporine A and/or pulse therapy with intravenous cyclophosphamide) and/or intravenous gammaglobulin.

This study was approved by the Research Ethics Committee at the HC-FMUSP, and the patients and/or their parents or guardians signed free and informed consent forms.

Univariate statistical analysis was performed using Fisher's exact test and the chi-square test to compare demographic data, and clinical, laboratory and treatment characteristics between the two study groups: with and without calcinosis. Student's *t* test for unpaired samples was used to compare mean age at disease onset for the two groups. The multivariate analysis employed backward stepwise logistic regression. Those independent variables that exhibited a level of statistical significance $\leq 5\%$ were chosen for the multivariate analysis model. The level of significance was set at 5% for all tests.

Results

The principal clinical, laboratory and treatment characteristics of the 54 JDM patients are given in Table 2.

Clinical and/or radiographic calcinosis was present in 23 (43%) patients, 15 (65%) females and eight (35%) males. This had already appeared before JDM was diagnosed in six (26%) cases, and in one of these it was the initial manifestation of the disease. In these cases, the median time between calcinosis and diagnosis of JDM was 9 months (variation of 15 days to 2 years). The deposits appeared after diagnosis in 17 (74%) patients. Calcinosis were predominantly located in the soft tissues of upper limbs, observed in 18 (78%) patients; followed by lower limbs in 13 (56.5%); the trunk in three (13%); scrotal and testicular region in two (8.7%) and urethral area in one (4.3%). Calcinosis circumscripta affected 15 (65%) patients, three had calcinosis universalis (13%) and there were extensive calcium deposits all over the surface of the bodies of five patients (22%).

Calcinosis was associated with persistent ulcerations in four (17%) patients, with recurrent secondary infections with

Table 2 - Clinical, laboratory and treatment characteristics of 54 patients with juvenile dermatomyositis

Variables	n = 54 (%)
Female sex	40 (74)
Muscle strength levels I, II or III	27 (50)
Muscle strength level IV	27 (50)
↑ CK	25 (46)
↑ AST	38 (70)
↑ ALT	32 (59)
↑ LDH	46 (85)
Pulmonary involvement	15 (27)
Cardiac involvement	8 (15)
Gastrointestinal involvement	22 (40)
Treated with prednisone	54 (100)
Treated with one or more immunosuppressor	25 (46)

ALT = aspartate alanine transferase; AST = aspartate aminotransferase; CK = creatine phosphokinase; LDH = lactate dehydrogenase.

piodermitis or abscesses in five cases (22%) and with articular contractures in five (22%). Calcium was liberated in a form similar to "chalk-powder" in three (13%) cases.

The initial treatment given to the patients with calcinosis to control their JDM was corticosteroids (prednisone and/or pulse therapy with methylprednisolone) in all cases. It proved necessary to add chloroquine diphosphate or hydroxychloroquine sulphate in four (17.3%) cases and one or more immunosuppressor was prescribed for 16 (69.5%): methotrexate in eight cases (34.7%), cyclosporine A in seven (30%) and pulse therapy with cyclophosphamide in one case (4.3%). Intravenous gammaglobulin was indicated for four patients (17.3%), thalidomide for one (4.3%) and D-penicillamine was given to one patient (4.3%).

Furthermore, 15 of the 23 patients were given specific treatment for calcinosis: diltiazem in six cases (26%), ethylenediaminetetraacetic acid (EDTA) in five (22%) and alendronate in four (17.3%) cases. Corticosteroid (triamcinolone hexacetonide) infiltration of the calcinosis was attempted with one patient. Surgical excision only proved necessary for the patient who developed calcinosis on the urethra.

The clinical, laboratory and treatment characteristics associated with the presence of calcinosis are given in Tables 3 and 4.

The univariate analysis demonstrated that cardiac ($p = 0.01$) and pulmonary ($p = 0.02$) involvement and the need for one or more immunosuppressor (methotrexate, cyclosporine A and/or pulse therapy with intravenous cyclophosphamide) to treat JDM ($p = 0.02$) were associated with increased frequency of calcinosis (Table 3). None of the patients with pulmonary involvement had the anti-Jo-1 antibody.

The multivariate analysis by logistic regression took the presence of calcinosis as dependent variable and the independent variables cardiac involvement, pulmonary involvement and treatment with one or more immunosuppressor. This statistical analysis demonstrated that cardiac involvement ($p = 0.018$; OR = 15.56; 95%CI 1.59-152.2) and the use of one or more of the immunosuppressors listed above ($p = 0.037$; OR 4.01; 95%CI 1.08-14.87) were the only independent variables associated with the presence of calcinosis (Table 4).

Calcinosis had no associations with demographic data. Age over 6.5 years (the mean age at onset) at disease onset was observed in 12 (52%) patients with calcinosis as against 19 (61%) without calcinosis ($p = 0.25$). A period of more than 1 year (the mean duration observed) between onset of the disease and diagnosis elapsed in 11 (48%) cases with calcinosis compared with four (13%) without calcinosis ($p = 0.31$).

Further to this there were no statistical differences between the groups with and without calcinosis in terms of:

Table 3 - Univariate analysis of demographic, clinical, laboratory and treatment characteristics associated with calcinosis in 54 patients with juvenile dermatomyositis

Characteristics, n (%) or mean $\pm$ SD	Calcinosis (n = 23)	No calcinosis (n = 31)	p
Female sex	16 (70)	25 (81)	0.34
Age at diagnosis in years	6.56 $\pm$ 2.6	7.41 $\pm$ 2.78	0.37
Time between disease onset and start of treatment, in years	1.0 $\pm$ 1.7	0.64 $\pm$ 0.88	0.34
Muscle strength levels I, II or III	12 (52)	15 (48)	1.0
Muscle strength level IV	11 (48)	16 (52)	1.0
$\uparrow$ CK	7 (30)	18 (58)	0.09
$\uparrow$ AST	15 (65)	23 (74)	0.32
$\uparrow$ ALT	13 (57)	19 (61)	1.0
$\uparrow$ LDH	19 (83)	25 (81)	1.0
Pulmonary involvement	10 (43)	5 (16)	0.02
Cardiac involvement	7 (30)	1 (3)	0.01
Gastrointestinal involvement	9 (39)	13 (42)	0.33
Treated with one or more immunosuppressor	15 (65)	10 (32)	0.02
Deaths	2 (8.7)	2 (6.4)	1.0

ALT = aspartate alanine transferase; AST = aspartate aminotransferase; CK = creatine phosphokinase; LDH = dehydrogenase lactate; SD = standard deviation.

Table 4 - Multivariate analysis model using logistic regression of variables associated with calcinosis in 54 patients with juvenile dermatomyositis

Dependent variable	Independent variable	OR (95%CI)	Nagelkerke's R ²	p
Calcinosis	Cardiac involvement	15.56 (1.59-152.2)	0.288	0.018
	Treatment with one or more IS	4.01 (1.08-14.87)		0.037

95%CI = 95% confidence interval; IS = immunosuppressors; OR = odds ratio.

female sex (70 vs. 81%; $p = 0.34$), initial muscle weakness (stages I, II or III: 52 vs. 48%, $p = 1.0$; stage IV: 48 vs. 52%, $p = 1.0$), elevated serum levels of muscle enzymes: CK, AST, ALT and LDH (30 vs. 58%; $p = 0.09$; 65 vs. 74%; $p = 0.32$; 57 vs. 61%; $p = 1.0$ and 83 vs. 81%; $p = 1.0$; respectively) or gastrointestinal involvement (39 vs. 42%; $p = 0.33$) (Table 3).

Four of the 54 patients with JDM (7%) died and underwent autopsies, two in each group ($p = 1.0$). One of the two patients who had had calcinosis died due to sepsis and the other from multiple perforations secondary to gastrointestinal vasculitis. Both of the deaths of patients without calcinosis were due to sepsis.

Discussion

This study analyzed 54 patients with JDM from a tertiary specialist pediatric rheumatology center. The clinical manifestations and laboratory findings indicative of JDM observed in this sample were similar to what has been described in the medical literature: reduced muscle strength (91.4-100%), elevated muscle enzyme levels (94-100%), pulmonary involvement (14.3-30%) and cardiac involvement (8.5-36%).^{8,11} However, in this sample, evidence of gastrointestinal involvement was observed in 40% of the population in contrast with the 17.1 to 26% described in the literature.^{8,11}

Calcinosis affects between 10 and 70% of patients with JDM.^{8,11,12} Our study identified this disorder in 43% of the patients and it was associated with severe cases of the disease, where there was cardiac involvement and immunosuppressors had been required.

Dystrophic calcifications are calcium deposits that appear in subcutaneous tissue, muscles, fascia and tendons, with a preference for the upper and lower limbs and traumatized areas, as demonstrated by this population.¹⁸ In this study calcinosis cutis circumscripta predominated, in agreement with the literature.^{10,20} One relevant feature was the presence of calcinosis all over the body surface, which had occurred in 1/5 of all cases. These diffuse deposits are associated with severe and long-term cases.^{10,18}

As was observed here, calcinosis may precede the diagnosis of JDM, but is generally most common between the first and third years of the disease. Nevertheless, there is a report

of calcinosis emerging 12 years after onset of the inflammatory myopathy.²¹

The etiopathogenesis of calcinosis in JDM is unknown, and to date there are few studies in the medical literature on this aspect. Macrophages and proinflammatory cytokines, such as IL-6, IL-1 and TNF- α , have been observed in calcium fluids.²² In 2000, Pachman et al.²³ studied the genetic polymorphism of TNF- α and detected that the allele TNF- α -308A was associated with dystrophic calcifications, a prolonged disease course and an elevated level of this proinflammatory cytokine. Recently, in 2006, Pachman et al.,²⁴ studied five cases of calcinosis of JDM. They investigated calcinosis and reported finding bone proteins, osteopontin, osteonectin and bone sialoprotein in protein extracts while the only mineral identified was hydroxyapatite. Nevertheless, the tissue making up the dystrophic calcifications was distinct from bone, with a high mineral content and an irregular mineral distribution.

Just one study has evaluated the risk factors associated with dystrophic calcification, using univariate and multivariate analysis models. Fisler et al.¹⁷ studied 35 cases and found evidence that calcinosis was associated with delayed diagnosis and start of treatment, increased muscle enzyme levels and prolonged disease duration. Pachman et al.²⁵ also observed an association between calcinosis and delays in starting treatment. In our study, despite the increased time observed between onset of signs and symptoms and institution of therapy, there was no significant difference between patients with and without in terms of this variable. Nevertheless, calcinosis was associated with systemic involvement and the use of aggressive treatment.

Our univariate analysis demonstrated that the presence of cardiac involvement, pulmonary involvement and use of immunosuppressors were all factors associated with calcinosis. However, the logistic regression model revealed that only cardiac involvement and prescription of cytotoxic agents were independent variables with significance for predicting calcinosis.

There are few descriptions of the cardiac involvement of JDM, although it is known that myocarditis, pericarditis and conductive disorders can occur.^{8,11,25-28} Furthermore,

descriptions of cardiac involvement associated with calcinosis are even rarer.²⁹ In this study, the manifestations of cardiac involvement observed were myocarditis and pericarditis, at disease onset, during activity. No cases involved congestive heart failure or conduction disorders. The association between calcinosis and cardiac involvement is probably due to their both being manifestations of a severe form of the disease with persistent inflammation.

Corticoid therapy is the first therapeutic option for treating active JDM, with a favorable response in 80% of patients.^{1,8,10-12,17,30} However, immunosuppressors and intravenous gammaglobulin are drugs that can alter the course of the disease and can be indicated during the initial stages of treatment, with the objective of improving control over disease activity and of reducing the chances of calcinosis emerging; which is how they were used with the majority of patients in this sample. Furthermore, it was also demonstrated that the use of cytotoxic drugs was associated with the development of calcinosis, probably because the same patients had severe forms of the disease and needed these medications.^{17,25-32}

The treatment of calcinosis is itself controversial, since spontaneous involution of the condition can even occur.^{10,29} Reports exist of good efficacy and absent or rare adverse events being obtained with EDTA, diltiazem and bisphosphonates (alendronate or pamidronate), and also with surgical excision and localized infiltration of triamcinolone hexacetonide,^{18,26-33} as was used with some of the patients studied here.

Another aspect worthy of interest was the mortality observed in this sample, caused by infection and systemic disease activity. Autopsy results showed that 5.5% of the JDM patients died from sepsis. One patient complained of recurrent abdominal pains and, at autopsy, there was evidence vasculitis of the mucosa, submucosa and serosa with ulceration and perforation of the gastrointestinal tract. In the literature this last symptom is described as occurring in up to 14% of patients with the disease.³⁴

One limitation to this study was the retrospective assessment of the medical records from a single tertiary pediatric rheumatology clinic, covering 16 consecutive years. Additionally, the extremely wide confidence intervals may reflect the small sample size, which is itself a function of the rarity of this disease.

Recently, scales to assess disease activity – the Disease Activity Score (DAS),³⁵ muscle strength – the Childhood Myositis Assessment Scale (CMAS) and the Manual Muscle Testing (MMT) system³⁶ – and supplementary assessment tests (capillaroscopy and magnetic resonance imaging)³⁷ have been used by pediatric rheumatologists to assess JDM. Prospective studies should be carried out to assess the association between calcinosis and disease activity as measured by these instruments.

In conclusion, calcinosis was a frequent finding with JDM and emerged during disease progression. The manifestation was associated with the more severe cases, those that also exhibited cardiac involvement and required immunosuppressant treatment.

Acknowledgements

We are grateful to Dr. Luciana B. Paim for her help with reviewing medical records, and to Prof. Dr. Claudio Leone for help with the statistical analysis.

References

1. Cassidy JT, Lindsley CB. Juvenile dermatomyositis. In: Cassidy JT, Petty RE, Laxer RM, Lindsley CB. Textbook of pediatric rheumatology. 5th ed. Philadelphia: Elsevier Saunders; 2005. p. 407-41.
2. Ansell BM. Juvenile dermatomyositis. Rheum Dis Clin North Am. 1991;17:931-42.
3. Ansell BM. Juvenile dermatomyositis. J Rheumatol Suppl. 1992; 33:60-2.
4. Mastaglia FL, Ojeda VJ. Inflammatory myopathies: Part 1. Ann Neurol. 1985;17:215-27.
5. Mastaglia FL, Ojeda VJ. Inflammatory myopathies: Part 2. Ann Neurol. 1985;17:317-23.
6. Miller FW. Inflammatory myopathies. Annual Review Course 55th Annual Scientific Meeting; 1991 Nov; Boston: Massachusetts; 1991.
7. Mendez EP, Lipton R, Ramsey-Goldman R, Roettcher P, Bowyer S, Dyer A, et al. US incidence of juvenile dermatomyositis, 1995-1998: results from the National Institute of Arthritis and Musculoskeletal and Skin Disease Registry. Arthritis Rheum. 2003;49:300-5.
8. Sogabe T, Silva CA, Kiss MHB. Clinical and laboratory characteristics of 50 children with dermato/polymyositis. Rev Bras Reumatol. 1996;36:351-9.
9. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med. 1975;292:344-7.
10. Bowyer SL, Blane CE, Sullivan DB, Cassidy JT. Childhood dermatomyositis: factors predicting functional outcome and development of dystrophic calcification. J Pediatr. 1983; 103:882-8.
11. Sallum AM, Kiss MH, Sachetti S, Resende MB, Moutinho KC, Carvalho Mde S, et al. Juvenile dermatomyositis: clinical, laboratorial, histological, therapeutical and evolutive parameters of 35 patients. Arq Neuropsiquiatr. 2002;60:889-99.
12. Plotz PH, Rider LG, Tragoff IN, Raben N, O'Hanlon TP, Miller FW. NIH conference. Myositis: immunologic contributions to understanding cause, pathogenesis, and therapy. Ann intern Med. 1995;122:715-724.
13. Pachman LM, Boskey AL. Clinical manifestations and pathogenesis of hydroxyapatite crystal deposition in juvenile dermatomyositis. Curr Rheumatol Rep. 2006;8:236-43.
14. Crowe WE. Dermatomyositis and polymyositis In: Gershwin ME, Robbins DL. Musculoskeletal diseases of children. New York: Grune & Stratton; 1983. p. 113-37.

15. Burgos-Vargas R, Vasquez-Mellado J, Gomez-Gordillo Y, Katona G. [Estudio clinico de la polidermatomiositis de inicio en la infancia](#). Bol Med Hosp Infant Mex. 1987;44:463-70.
16. Miller LC, Michael AF, Kim Y. [Childhood dermatomyositis](#). Clinical course and long-term follow-up. Clin Pediatr (Phila). 1987; 26:561-6.
17. Fisler RE, Liang MG, Fuhlbrigge RC, Yalcindag A, Sundel RP. [Aggressive management of juvenile dermatomyositis results in improved outcome and decreased incidence of calcinosis](#). J Am Acad Dermatol. 2002;47:505-11.
18. Rider LG. Calcinosis in juvenile dermatomyositis: pathogenesis and current therapies. Pediatric Rheumatology Online Journal. <http://www.pedrheumonlinejournal.org>. Access: 23/07/2007.
19. Medical Research Council. Aids to the investigation of peripheral nerve injuries. 2nd ed. London: Majesty's Stationery; 1943.
20. Black AS, Kanat IO. [A review of soft tissue calcifications](#). J Foot Surg. 1985;24:243-50.
21. Wananukul S, Pongprasit P, Wattanakrai P. [Calcinosis cutis presenting years before other clinical manifestations of juvenile dermatomyositis: report of two years](#). Australas J Dermatol. 1997;38:202-5.
22. Mukamel M, Horev G, Mimouni M. [New insight into calcinosis of juvenile dermatomyositis: a study of composition and treatment](#). J Pediatr. 2001;138:763-6.
23. Pachman LM, Liotta-Davis MR, Hong DK, Kinsella TR, Mendez EP, Kinder JM, et al. [TNFalpha-308A allele in juvenile dermatomyositis: association with increased production of tumor necrosis factor alpha, disease duration, and pathologic calcifications](#). Arthritis Rheum. 2000;43:2368-77.
24. Pachman LM, Veis A, Stock S, Abbott K, Vicari F, Patel P, et al. [Composition of calcifications in children with juvenile dermatomyositis: association with chronic cutaneous inflammation](#). Arthritis Rheum. 2006;54:3345-50.
25. Pachman LM, Abbott K, Sinacore JM, Amoroso L, Dyer A, Lipton R, et al. [Duration of illness is an important variable for untreated children with juvenile dermatomyositis](#). J Pediatr. 2006;148:247-53.
26. Romero KT, Terreri MT, Len CA, Hilário MO. [Dermatomiosite e polimiosite juvenis: diagnóstico e tratamento](#). Rev Paul Pediatr. 2003;21:223-7.
27. Pilkington CA, Wedderburn LR. [Paediatric idiopathic inflammatory muscle disease: recognition and management](#). Drugs. 2005;65:1355-65.
28. Compeyrot-Lacassagne S, Feldman BM. [Inflammatory myopathies in children](#). Pediatr Clin North Am. 2005;52:493-520, vi-vii.
29. Ostrov BE, Goldsmith DP, Eichenfield AH, Athreya BH. [Hypercalcemia during the resolution of calcinosis universalis in juvenile dermatomyositis](#). J Rheumatol. 1991;18:1730-4.
30. Reed AM, Lopez M. [Juvenile dermatomyositis: recognition and treatment](#). Paediatr Drugs. 2002;4:315-21.
31. Stringer E, Feldman BM. [Advances in the treatment of juvenile dermatomyositis](#). Curr Opin Rheumatol. 2006;18:503-6.
32. Ramanan AV, Campbell-Webster N, Ota S, Parker S, Tran D, Tyrrell PN, et al. [The effectiveness of treating juvenile dermatomyositis with methotrexate and aggressively tapered corticosteroids](#). Arthritis Rheum. 2005;52:3570-8.
33. Castro TC, Yamashita E, Terreri MT, Len CA, Hilário MO. [Calcinose na infância, um desafio terapêutico](#). Rev Bras Reumatol. 2007; 47:63-8.
34. Downey EC Jr., Woolley MM, Hanson V. [Required surgical therapy in the pediatric patient with dermatomyositis](#). Arch Surg. 1988;123:1117-20.
35. Bode RK, Klein-Gitelman MS, Miller ML, Lechman TS, Pachman LM. [Disease activity score for children with juvenile dermatomyositis: reliability and validity evidence](#). Arthritis Rheum. 2003;49:7-15.
36. Huber AM, Feldman BM, Rennebohm RM, Hicks JE, Lindsley CB, Perez MD, et al. [Validation and clinical significance of the Childhood Myositis Assessment Scale for assessment of muscle function in the juvenile idiopathic inflammatory myopathies](#). Arthritis Rheum. 2004;50:1595-603.
37. Brown VE, Pilkington CA, Feldman BM, Davidson JE; Network for Juvenile Dermatomyositis, Paediatric Rheumatology European Society (PReS). [An international consensus survey of the diagnostic criteria for juvenile dermatomyositis \(JDM\)](#). Rheumatology (Oxford). 2006;45:990-3.

Correspondence:

Adriana Maluf Elias Sallum
 Av. Juriti, 187/21
 CEP 04520-000 – São Paulo, SP – Brazil
 E-mail: adrimaluf@icr.hcnet.usp.br

CASE REPORT

Irreversible blindness in juvenile systemic lupus erythematosus

RT Almeida¹, NE Aikawa^{1,2}, AME Sallum¹, AA Jesus¹, LCF Sa³ and CA Silva^{1,2}

¹Pediatric Rheumatology Unit, Children's Hospital, Hospital das Clínicas da Faculdade de Medicina da Universidade São Paulo, São Paulo, Brazil; ²Division of Rheumatology, Hospital das Clínicas da Faculdade de Medicina da Universidade São Paulo, São Paulo, Brazil; and ³Ophthalmology Unit, Children's Hospital, Hospital das Clínicas da Faculdade de Medicina da Universidade São Paulo, São Paulo, Brazil

Blindness caused by severe vasculitis or uveitis is rare in juvenile systemic lupus erythematosus (JSLE) patients. In a 27-year period, 5367 patients were followed at our Paediatric Rheumatology Division and 263 (4.9%) patients had JSLE (American College of Rheumatology criteria). Of note, two (0.8%) of them had irreversible blindness. One of them presented with cutaneous vasculitis and malar rash, associated with pain and redness in both eyes, impairment of visual acuity due to iridocyclitis and severe retinal vasculitis with haemorrhage. Another patient had peripheral polyneuropathy of the four limbs and received immunosuppressive drugs. Three weeks later, she developed diffuse herpes zoster associated with acute blindness due to bilateral retinal necrotizing vasculitis compatible with varicella zoster virus ocular infection. Despite prompt treatment, both patients suffered rapid irreversible blindness. In conclusion, irreversible blindness due to retinal vasculitis and/or uveitis is a rare and severe lupus manifestation, particularly associated with disease activity and viral infection. *Lupus* (2011) 20, 95–97.

Key words: Retinal vasculitis; uveitis; blindness; juvenile systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a rare autoimmune disorder that may affect multiple organs and systems, including ophthalmic involvement.^{1,2} Although paediatric lupus patients may have ocular manifestations occurring in the course of the disease, blindness has been rarely described.²

All components of the visual system can be affected by ischemic and inflammatory processes in SLE due to antiphospholipid syndrome, disease activity or infections. Visual loss may result from retinopathy with microangiopathy, retinal vaso-occlusive disease, optic neuritis, uveitis, scleritis, cataract and glaucoma in lupus patients, and it may vary from transient and mild visual loss to irreversible blindness.^{2–4}

Of note, a few case reports have shown retinal vasculitis leading to irreversible blindness in juvenile SLE (JSLE) patients.^{3,4} However, prevalence of blindness in the lupus paediatric population has not been studied. Therefore, from January

1983 to December 2009, 5367 patients were followed at the Paediatric Rheumatology Unit of the Instituto da Criança da Faculdade de Medicina da Universidade de São Paulo and 263 (4.9%) of them met the American College of Rheumatology (ACR)⁵ classification criteria for JSLE. Two of them (0.8%) had irreversible bilateral blindness due to retinal vasculitis and/or severe uveitis and were reported.

Case reports

Case 1

In June 2004, a 15-year old girl was diagnosed with JSLE due to malar rash, proteinuria 1 g/day, pericarditis, bilateral pleural effusion, antinuclear antibodies (ANA) 1:160 and positive anti-double stranded DNA (anti-dsDNA). Immunological tests were negative for the following serum antibodies: anti-Sm, anti-RNP, anti-Ro, anti-La, lupus anticoagulant and anticardiolipin IgM and IgG. At this time, the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)⁶ was 12 and she was treated with intravenous methylprednisolone and later with prednisone (1 mg/kg/day) and

Correspondence to: Clovis Artur Almeida da Silva, Rua Araíoses, 152/81 Vila Madalena, São Paulo, SP, Brazil, CEP – 05442-010

Email: clovis.silva@icr.usp.br

Received 16 May 2010; accepted 15 June 2010

hydroxychloroquine (5 mg/kg/day) with improvement of these manifestations. In July 2004, she suffered from cutaneous vasculitis on her feet, malar rash and acute confusional state. In addition, she had photophobia, pain and redness in both eyes and impairment of visual acuity, which required hospitalization. Laboratory examinations revealed hemoglobin 8 g/L, hematocrit 23%, white blood cell count 16,400 (72% neutrophils, 24% lymphocytes and 4% monocytes), platelets 142,000/mm³, reticulocytes 1.9%, urinalysis (5000 leukocytes and 64,000 erythrocytes), C3 0.82 g/L (normal 0.5–1.8), C4 0.05 g/L (normal 0.1–0.4), erythrocyte sedimentation rate (ESR) 48 mm for the first hour (normal < 20), C-reactive protein (CRP) 3.2 mg/dL (normal < 5), urea 38 mg/dL (normal 10–42) and creatinine 0.7 mg/dL (normal 0.6–0.9). Renal biopsy showed focal and segmental lupus nephritis [class III of World Health Organization (WHO) classification]. On admission, she was promptly evaluated by an ophthalmologist, who evidenced a severe bilateral anterior chamber inflammatory process (inflammatory debris and retinal hyphema) on slit-lamp examination and severe retinal vasculitis with haemorrhage. Her visual acuity was lower than 20/200 in both eyes. Ocular ultrasonography showed vitreous opacities, diffuse thickening, irregularity of the posterior chamber and retinal vasculitis. The SLEDAI-2K⁶ was 20. Prednisone eye drops were administered every hour, atropine eye drops every 6 hours and phenylephrine eye drops every 12 hours. She was promptly treated with three pulses of intravenous methylprednisolone therapy and intravenous cyclophosphamide (750 mg/m²/month). Ten days after admission, her visual acuity remained unchanged. Ocular examination showed bilateral eyelid edema, irregular pupil and cataract. Slit-lamp examination revealed conjunctival injection, anterior chamber activity cells grade 4+, flare grade 4+ associated with bilateral hypopyon and severe retinal vasculitis with diffuse haemorrhage. The intraocular pressure was 5 mmHg. In spite of six consecutive intravenous cyclophosphamide (1000 mg/m²/month) associated with intravenous methylprednisolone and azathioprine, there was no improvement in her visual acuity and she remained legally blind.

Case 2

A 20-year old female was diagnosed with JSLE at the age of seven due to malar rash, arthritis, ANA 1:2560, proteinuria 1.5 g/day and diffuse proliferative glomerulonephritis according to the WHO classification. She was treated with corticosteroids,

intravenous cyclophosphamide and hydroxychloroquine. In 2005, aged 19, she suffered lower limb edema and macroscopic hematuria. During this time, the laboratory examinations revealed: hemoglobin 14 g/L, hematocrit 40%, white blood cell count 24,000/mm³ (67% neutrophils, 24% lymphocytes, 5% monocytes, 4% eosinophils), platelets 260,000/mm³, ESR 30 mm in the first hour and CRP 4.21 mg/dL. Immunological tests were positive for the following serum antibodies: ANA 1:1280, anti-RNP, anti-dsDNA, anticardiolipin (IgM 15 MPL and IgG 30 GPL), lupus anticoagulant and antiribosomal P protein. C3 was 0.15 g/L, C4 0.05 g/L, proteinuria 2.16 g/day, urea 40 mg/dL, creatinine 0.8 mg/dL and urinalysis (leukocytes 100,000/mL and erythrocytes 12,000/mL). The SLEDAI-2K⁶ was 16 and she was treated with intravenous methylprednisolone and mycophenolate mofetil (2 g/day). One month later, she had lower and upper limbs muscle weakness (grade III according to the Medical Research Council®), hyporeflexia, and hyperesthesia, and the electro-neuromyography showed chronic demyelinating peripheral polyneuropathy in all four limbs. At this time, immunological tests were negative for lupus anticoagulant, IgM and IgG anticardiolipin antibodies in two different weeks, and she was treated with intravenous methylprednisolone and cyclophosphamide (1000 mg/m²/month). Two weeks later she developed diffuse herpes zoster. Concomitantly, she suffered an acute bilateral amaurosis associated with increasingly blurry vision and intense photophobia. Ophthalmologic exam showed bilateral retinal necrotizing vasculitis compatible with varicella zoster virus ocular infection. She received intravenous immunoglobulin (2 g/kg/dose), intravenous acyclovir and two doses of intravitreal gancyclovir. Despite treatment, she remained legally blind with a visual acuity of 20/200 in both eyes. Two months later, she died of septic shock.

Discussion

To our knowledge, this is the first study that has evaluated the prevalence of irreversible blindness in a large population of JSLE in a tertiary Paediatric University Hospital and that showed a rare frequency of this severe manifestation. This ophthalmic involvement was associated with disease activity and varicella zoster virus infection.

Retinopathy is the main cause of visual impairment in active SLE patients, and ocular findings

include retinal haemorrhages, vasculitis, cotton wool spots and hard exudates, all related to vascular damage.^{2,7} This complication was previously associated with the presence of neuropsychiatric involvement and higher SLEDAI score,^{7,8} as observed herein in both cases. Moreover, severe and acute panuveitis resulting in blindness is a rare ocular manifestation in lupus patients.^{2,9}

Our patients suffered from severe visual loss and were considered legally blind. In fact, according to the WHO, the criteria of legal blindness are a visual acuity of 20/200 (6/60) in the better eye or a visual field constriction to 20 degrees or less (tunnel vision) in the better eye.¹⁰

In addition, significant visual impairment is seen in cases of extensive narrowing of larger retinal vessels, as evidenced in one of our cases. Of note, early visual involvement was also observed in the course of JSLE.^{3,4} The mainstay of ocular treatment due to lupus flare by severe vasculitis or uveitis is the use of intravenous methylprednisolone and immunosuppressive drugs, which could attain minor or moderate improvement and stabilization of visual acuity.^{3,4,8} Despite early treatment, our patients did not improve, possibly due to the severity of the disease.

Remarkably, infection is the main cause of morbidity and mortality in our Brazilian population of paediatric lupus, including viral infections such as herpes zoster.¹ Varicella zoster virus infection could be associated with acute and progressive retinal necrosis as observed in our second case. This severe ophthalmic manifestation occurs mainly in immunosuppressed patients. Bilateral involvement occurs in two-thirds of patients with this infection and treatment includes intravenous acyclovir and ganciclovir.¹¹ Intravenous immunoglobulin together with antiviral therapy was used to minimize damage to the optic nerve and retinal blood vessels. Despite these treatments, the visual prognosis of acute retinal necrosis is still poor.¹¹ Of concern is that this was the first case reported in a lupus patient leading to irreversible blindness due to acute varicella zoster virus infection, thus

reinforcing the importance of future clinical trials with herpes zoster vaccine in lupus patients.

In conclusion, irreversible blindness due to retinal vasculitis and/or uveitis is a rare lupus manifestation, particularly associated with disease activity and viral infection. This study reinforces the importance of an early diagnosis and an early introduction of aggressive treatment, despite the poor prognosis.

Funding

This study was sponsored by Conselho Nacional de Desenvolvimento Científico - CNPQ (300248/2008-3 to CAS) and Federico Foundation to CAS.

References

- 1 Facó MM, Leone C, Campos LM, Febrônio MV, Marques HH, Silva CA. Risk factors associated with the death of patients hospitalized for juvenile systemic lupus erythematosus. *Braz J Med Biol Res* 2007; 40: 993–1002.
- 2 Al-Mayouf SM, Al-Hemidan AI. Ocular manifestations of systemic lupus erythematosus in children. *Saudi Med J* 2003; 24: 964–966.
- 3 Ho TY, Chung YM, Lee AF, Tsai CY. Severe vaso-occlusive retinopathy as the primary manifestation in a patient with systemic lupus erythematosus. *J Chin Med Assoc* 2008; 71: 377–380.
- 4 Bandyopadhyay SK, Moulick A, Dutta A. Retinal vasculitis - an initial presentation of systemic lupus erythematosus. *J Indian Med Assoc* 2006; 104: 526–527.
- 5 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 1725.
- 6 Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol* 2002; 29: 288–291.
- 7 Ushiyama O, Ushiyama K, Korada S, *et al.* Retinal disease in patients with systemic lupus erythematosus. *Ann Rheum Dis* 2000; 59: 705–708.
- 8 Au A, O'Day J. Review of severe vaso-occlusive retinopathy in systemic lupus erythematosus and the antiphospholipid syndrome: associations, visual outcomes, complications and treatment. *Clin Experiment Ophthalmol* 2004; 32: 87–100.
- 9 Kotaniemi K, Aho K, Kotaniemi A. Uveitis as a cause of visual loss in arthritides and comparable conditions. *J Rheumatol* 2001; 28: 309–312.
- 10 Dandona R, Dandona L. Refractive error blindness. *Bull World Health Org* 2001; 79: 237–243.
- 11 Bonfioli AA, Eller AW. Acute retinal necrosis. *Semin Ophthalmol* 2005; 20: 155–160.